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**ACE Inhibitor Therapy for Primary Prevention of Cardiovascular
Morbidity and Mortality in Patients with Type 2 Diabetes**

by



Dean T. Eurich

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment
of the requirements for the degree of Master of Science

in

Pharmaceutical Sciences

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ABSTRACT

Cardiovascular (CV) disease is the leading cause of morbidity and mortality in patients with type 2 diabetes. Using a retrospective cohort design, we evaluated the effects of ACE inhibitors on morbidity and mortality in patients with type 2 diabetes and no previous CV disease. From a population of 'new users' of oral antidiabetic agents, a cohort of 'new users' of ACE inhibitor therapy was identified. Individuals not receiving ACE inhibitors throughout the follow-up period were classified into the non ACE inhibitor cohort. Subjects with previously established CV disease were excluded. Multivariate Cox proportional hazards regression was used to assess differences in clinical outcomes between cohorts.

A total of 1,187 and 4,989 subjects were included in the ACE inhibitor and non ACE inhibitor cohorts, respectively. After a mean follow-up of 5.3 years, ACE inhibitor use was associated with a significant reduction in all cause-related mortality and CV-related morbidity and mortality.

"Few can foresee whither their road will

lead them, till they come to its end."

- Lord of the Rings, The Fellowship of the Ring, 2001

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CHAPTER 1: INTRODUCTION

1.1 Statement of the Problem

Diabetes mellitus (DM) is a common progressive metabolic disease characterized by chronic hyperglycemia.¹ Although the exact number of people affected by the disease is not known, it is estimated that 135 million people are affected with the disease worldwide.² In Canada, there are currently over 2 million Canadians affected with this condition and the number is expected to increase to 3 million by the year 2010.³ The burden on the health care system to treat and manage these patients is considerable. A person with diabetes incurs medical costs that are two to five times higher than those of a person without diabetes.³ Although there has been little research into the total economic cost of treating diabetes in Canada, a recent study indicated that the direct medical and indirect (lost productivity) costs of diabetes and its complications in Canada for 1998 was between \$4.76 - \$5.23 billion (in U.S. dollars).⁴

DM is not a single disease entity but rather a heterogeneous group of disorders with hyperglycemia as a unifying feature.¹ Although several distinct forms of DM exist, there are two major forms of the disease; referred to as type 1 DM and type 2 DM. Type 2 diabetes is the most common form of the disease affecting approximately 90 percent of all individuals with diabetes.³ The prevalence of type 2 diabetes dramatically increases with age, with approximately 15-20% of people above the age of 65 years being affected.²

The development of type 2 DM is associated with significant short and long-term health complications due to microvascular and macrovascular complications of the disease. In particular, macrovascular complications have a significant impact on

morbidity and mortality in people with diabetes. Consequently, it is not surprising that diabetes is a major risk factor for the development of cardiovascular diseases, including stroke, hypertension, and heart and vascular disease. The incidence of, and mortality from, cardiovascular disease and stroke is 2-3 times higher for men and 3-4 times higher for women with diabetes as compared to the general population.⁵⁻⁸ It has also been shown that the prevalence of coronary heart disease in white adults with diabetes is about 45% compared to only 25% in individuals without diabetes.⁹ The incidence of silent ischemia and myocardial infarction are also greater in people with diabetes than people without diabetes.¹⁰⁻¹² Unfortunately, people with diabetes experience a higher rate and severity of complications post myocardial infarction. People with diabetes have an increased risk of developing congestive heart failure, recurrent myocardial infarction, fatal arrhythmias, and have a lower survival rate as compared to people without diabetes post myocardial infarction.¹³ It has been estimated that approximately 44% of individuals with type 2 diabetes die within 10 years of diagnosis, and 70% of all deaths in type 2 DM can be attributed to cardiovascular disease.¹⁴⁻¹⁶

Due to the significant impact of cardiovascular disease on morbidity and mortality in people with or without diabetes, there are increasing efforts aimed at risk reduction. Cardiovascular disease is a largely preventable disease; however, it is an extremely complex undertaking. There are numerous risk factors for the development of cardiovascular disease and not all can be modified. Major modifiable risk factors include dyslipidemia, hypertension, diabetes, body weight, exercise, and smoking. There has been intense research attempting to improve these risk factors, particularly in diabetic subpopulations. In most situations, a combination of aggressive lifestyle modification and

drug therapy has been required to produce significant change. These aggressive strategies have resulted in a considerable reduction in the incidence of heart disease in the general population. These reductions, however, appear to be considerably smaller in people with diabetes and there is some evidence to suggest that the risk for cardiovascular disease may actually be increasing in women with diabetes.^{17,18}

Although the above mentioned risk factors contribute to a significant proportion for the development of cardiovascular disease, they do not fully account for all the risk. Over the last decade, there has been ongoing research to establish potential new novel risk factors for the development of cardiovascular disease. One such risk factor that has emerged is the role of the renin-angiotensin-aldosterone system (RAAS). There is increasing evidence from epidemiological and clinical trials suggesting that activation of the RAAS may play a significant role in the development of cardiovascular disease.¹⁹⁻²¹ Furthermore, large scale clinical trials suggest that angiotensin-converting enzyme (ACE) inhibitors can prevent or delay development of cardiovascular disease in certain subpopulations.²²⁻²⁹ This strongly suggests that a reduction in activity of the RAAS by ACE inhibitors could improve cardiovascular morbidity and mortality, independent of their effects on blood pressure or left ventricular remodelling.

Although there have been numerous large randomized controlled trials with ACE inhibitors in various cardiovascular diseases, the effects of ACE inhibition on the prevention of cardiovascular morbidity and mortality have not been clearly established.³⁰⁻³⁶ With the recent release of the HOPE study, however, it would appear that ACE inhibitors are effective agents in delaying and preventing major cardiovascular events in high risk patients.³⁷ Unfortunately, it still remains unclear whether ACE

inhibitors are as beneficial for the prevention of cardiovascular morbidity and mortality in people with diabetes. Although most of the major clinical trials, including the HOPE study, have included people with diabetes, the total number of people with diabetes studied with ACE inhibitors for cardiovascular disease prevention remains relatively small.

Further, the results of the HOPE study should be viewed as support for the use of ACE inhibitors for secondary prevention. Over 80 percent of the individuals enrolled in the HOPE study had a history of cardiovascular disease and over 50% of those individuals had a history of myocardial infarction.³⁷ These numbers are very similar to the baseline characteristics seen in the MICRO-HOPE sub-study, which focused on the diabetic subpopulation of the HOPE participants. In the MICRO-HOPE substudy, only approximately 30 percent of individuals had no previous cardiovascular disease prior to enrollment.²⁴ As well, only individuals 55 years of age or older were eligible to be included in the HOPE study and MICRO-HOPE substudy.^{24;37} As a result, it still remains unclear whether younger adults with diabetes, without pre-established cardiovascular disease, will benefit equally from ACE inhibitor therapy.

The administrative databases of Saskatchewan health provide a unique setting to evaluate the use of ACE inhibitors in patients with type 2 diabetes, without pre-established cardiovascular disease. Administrative databases are becoming an important source of evidence for evaluating the impact of health care interventions in today's practice.³⁸ Administrative databases often provide researchers with access to a large number of patients and significant patient follow-up years to evaluate health outcomes. Further, this large quantity of data can be collected in a relatively short period of time and

often at a lower expense as compared to conducting randomized controlled trials (RCTs). Although RCTs provide the best possible evidence for efficacy, they often provide little evidence for effectiveness due to the tight inclusion and exclusion criteria employed in RCTs. Since administrative data is collected from "real world" health care systems, administrative databases provide strong evidence for effectiveness, as well as, evidence for efficacy, although the evidence for efficacy is weaker than with RCTs. As well, depending on the nature of the question, RCTs may not always be feasible or ethical.

The evaluation of ACE inhibitor therapy for primary prevention in patients with type 2 diabetes falls into this scenario. To evaluate the use of ACE inhibitors using a RCT would be a complex undertaking. First, research has suggested that a significant proportion of individuals with type 2 diabetes have established cardiovascular disease at time of diagnosis of their diabetes.^{39,40} As a result, it would be extremely difficult to enrol a sufficiently large number of individuals with type 2 diabetes who do not already have established cardiovascular disease in a RCT setting. Second, if ACE inhibitor therapy was compared versus placebo therapy, once the patient develops cardiovascular disease it would be unethical to withhold ACE inhibitor therapy in patients who were randomized to the placebo arm based on the results of the HOPE and MICRO-HOPE studies. As a result, this type of research question cannot be easily addressed through a RCT and can be better addressed through an observational study design.

In summary, although cardiovascular morbidity and mortality in people with diabetes can be reduced by lowering blood pressure and lipids, there is very little evidence evaluating the effects of ACE inhibitors.^{24,27,39,41-43} The evidence currently available is from large randomized controlled trials with several limitations. First, most of

the trials have enrolled relatively few (< 20%) patients with diabetes and have been underpowered to evaluate the potential benefits of ACE inhibitors in patients with diabetes. Second, most of the trials have studied the effects of ACE inhibitors for secondary prevention only and it remains unclear as to the potential benefits of ACE inhibitors for primary prevention of cardiovascular disease. Third, most of the studies have not studied the effects of ACE inhibitors in patients of all ages with type 2 DM. The studies that have been completed have been very selective in the age category of patients who are included in the studies making it difficult to determine if the benefits of ACE inhibitors can be applied to all patients. Fourth, most of these trials have had relatively short follow-up periods. Fifth, all of the studies have used tight inclusion/exclusion criteria and thus it remains unclear whether these benefits can be applied to the larger, less controlled community setting. A large, population based study evaluating the long term use of ACE inhibitors on cardiovascular morbidity and mortality in patients of all ages with type 2 DM would address many of these limitations. In addition, a large, population based study can address this question more effectively and efficiently than with a RCT.

1.2 Objectives and Hypotheses

The purpose of this study was to evaluate the effects of ACE inhibitors on morbidity and mortality in patients with type 2 DM and no previous cardiovascular disease. Specific research objectives were to evaluate the effects of ACE inhibitors on:

1. all cause-related mortality;
2. cardiovascular-related mortality

3. non-fatal myocardial infarction and non-fatal stroke
4. combined endpoint consisting of cardiovascular-related mortality, non-fatal myocardial infarction, and non-fatal stroke.

We hypothesized that subjects with type 2 DM who receive ACE inhibitors would have a significant risk reduction in all cause-related mortality, cardiovascular-related mortality, non-fatal myocardial infarction and non-fatal stroke, and in the combined endpoint than subjects with type 2 DM who do not receive ACE inhibitors.

CHAPTER 2: REVIEW OF THE LITERATURE

2.1 Diabetes Mellitus

2.1.1 *Classification of Diabetes Mellitus*

Diabetes mellitus (DM) is a common chronic disease that affects more than 2 million people in Canada.³ Unfortunately, this number likely underestimates the true prevalence of DM in Canada. Research has suggested that for every person that is diagnosed with DM there is one person with undiagnosed DM, suggesting that over 10 percent of the Canadian population may have DM.^{3,44} It is also known that individuals aged 65 years or older are at an increased risk of developing DM. The prevalence of DM in individuals aged 65 years or older is three times higher compared to individuals 35-64 years of age.⁴⁵ Since the average age of our population is expected to markedly increase over the next decade, so too is the prevalence of DM.³

DM is a complex medical disorder characterized by hyperglycemia resulting from inappropriate insulin secretion, insulin action, or both.^{1,3} Clinically, diabetes presents as a mixture of symptoms including glucose intolerance and alterations in lipid and protein metabolism. These abnormalities, especially chronic hyperglycemia, are associated with significant long-term complications resulting in kidney, eye, nerve, heart and vascular system damage.^{1,3}

There are two primary etiological classifications of DM; insulin dependent DM (type 1 DM) and non-insulin-dependent DM (type 2 DM). Although the exact cause of DM is not known, several pathogenic processes have been identified in the development of DM. What is also known is that type 1 diabetes and type 2 diabetes arise due to very different defective processes within the body. Type 1 diabetes is primarily thought to

develop due to autoimmune destruction of the beta-cells in the pancreas, subsequently resulting in a deficiency of endogenous insulin production.⁴⁶ Although the trigger for the autoimmune destruction of the pancreatic beta-cells has not been definitively identified, it is hypothesised that cow's milk, viral, dietary or some other environmental exposure may be the cause.⁴⁷

Of the individuals affected with diabetes, type 1 diabetes represents a relatively small proportion (only 5 – 10 percent) of all diabetes cases.⁴⁵ Type 1 diabetes generally develops before 30 years of age with the highest incidence occurring during early childhood. As a result of this high incidence in childhood, type 1 diabetes was previously referred to as juvenile-onset diabetes.⁴⁶ Although the onset of type 1 diabetes peaks in childhood years, the age of onset of type 1 diabetes is quite variable in individuals and largely depends upon the rate of destruction of the pancreatic beta-cells.⁴⁸ Regardless of the age of onset, the clinical symptoms of type 1 diabetes generally develop quite rapidly in individuals ranging from a few days to a few months. Patients usually present clinically with polyuria, polydipsia, fatigue, weight loss and in severe cases ketoacidosis. Due to the destruction of the pancreatic beta-cells, individuals with type 1 diabetes require exogenous insulin therapy for survival.⁴⁶ Following the initial clinical diagnosis, many individuals enter into a phase known as the "honeymoon period". During this time, individuals often experience a remission of their diabetes and is associated with a marked decrease in the amount of exogenous insulin required to control their condition.^{45;49} Unfortunately, this phase lasts for only a few weeks or months. Eventually, however, individuals with type 1 diabetes become progressively dependent on exogenous insulin

therapy for survival and are increasingly susceptible to weight loss, infections, and potentially life-threatening ketoacidosis.^{1;3}

In contrast to type 1 diabetes, type 2 diabetes is a heterogeneous disorder which can result due to various underlying defective processes ranging from predominantly insulin resistance with relative insulin deficiency (rather than complete as seen in type 1 diabetes) to predominantly an insulin secretory defect with insulin resistance.^{1;3;50} Although the exact cause is unknown, type 2 diabetes does not involve autoimmune destruction of the pancreatic beta-cells. As a result, individuals with type 2 diabetes do not require exogenous insulin therapy to survive.^{1;3;50}

Generally, clinical presentation in individuals with type 2 diabetes is very different from individuals with type 1 diabetes. Unlike type 1 diabetes, often the onset and progression of type 2 diabetes occurs more slowly over months or years. Typically, type 2 diabetes is present 4-7 years prior to its clinical diagnosis and subsequent treatment.⁵¹ This delay in clinical diagnosis can result in significant morbidity and mortality.⁵² Although individuals with type 2 diabetes can present similarly as individuals with type 1 diabetes, which may include polyuria, polydipsia, and blurred vision, often the individual is asymptomatic due to the gradual onset of hyperglycemia.¹ Generally, ketoacidosis is not of a concern in individuals with type 2 diabetes as the pancreas can generally secrete enough insulin to prevent ketoacidosis from occurring.⁴⁹

There are numerous environmental and genetic risk factors associated with the development of type 2 diabetes. The risk of developing type 2 diabetes dramatically increases in individuals who are engaged in what is known as the 'diabetogenic lifestyle'. This lifestyle includes excessive caloric intake, decreased caloric expenditure, obesity,

and lack of physical activity.¹ Obesity or a high percentage of abdominal adipose tissue is one of the main pathophysiological features associated with type 2 diabetes.¹ Other modifiable risk factors include hypertension, dyslipidemia, and cigarette smoking.³ There is also a strong genetic predisposition associated with type 2 diabetes. Individuals with advanced age, positive family history, impaired fasting glucose, impaired glucose tolerance, certain ethnic backgrounds (especially Aboriginal, Black and Hispanic), and women with prior gestational diabetes mellitus or polycystic ovary syndrome are at a greater risk for the development of type 2 diabetes.^{45;53;54}

Although various defective processes are potentially responsible for the development of type 2 diabetes, type 2 diabetes is predominately characterized by insulin resistance.⁵⁰ Insulin resistance leads to several undesirable effects within the body depending upon the organ system affected. Generally, insulin resistance presents as increased hepatic glucose production, increase in lipolysis within the adipose tissue, and decreased glucose uptake, especially within skeletal muscle.^{49;55} Insulin resistance is present far in advance of any clinical signs or symptoms of overt diabetes.⁵⁶ Initially, early in the progression of the disease, the body is able to overcome the effects of insulin resistance by increasing pancreatic insulin secretion from the beta-cells. Over time, however, beta-cell function begins to deteriorate. Eventually, the pancreas is unable to produce sufficient insulin levels to overcome the detrimental effects of the insulin resistance which results in chronic hyperglycemia.⁵⁷

Research has also shown that there is a strong relationship between insulin resistance in type 2 diabetes and a variety of other disorders including central obesity, atherosclerosis, hypertriglyceridemia, low high-density lipoprotein cholesterol levels, and

hypertension.⁵⁵ This collection of abnormalities and insulin resistance has collectively be termed the 'insulin resistance syndrome', also known as 'the metabolic syndrome', the 'dys-metabolic syndrome' or 'syndrome X'.⁵⁵

2.1.2 Management of Type 2 Diabetes Mellitus

Since diabetes is a multifaceted disease, interventions to improve the health of individuals with diabetes must address a wide range of factors and should not only focus on glycemic control. Both the Canadian and U.S. Guidelines for the management of diabetes mellitus indicate that the primary goal of therapy is to reduce the short and long term microvascular and macrovascular complications of the disease, to reduce and control symptoms, to reduce mortality, and to improve the patient's quality of life and sense of well-being.^{3;58} In order to achieve these goals, management programs should include therapy directed at glycemic control, risk factor adjustment (especially lipids and hypertension), complications monitoring, lifestyle modifications (diet and exercise), and potential pharmacological therapy.^{3;58}

Normalization of glucose levels is one of the fundamental aspects of any management program for DM. Randomized controlled trials have shown that achieving glycemic control is associated with reduced microvascular complications in individuals with type 2 diabetes.^{39;59} It has been recommended that management programs should strive to achieve a HbA_{1C} target of <7% although the target goal must be tailored to each individual.^{3;58}

Dietary modification and exercise programs are integral components of all type 2 diabetes management programs. Irrespective of weight loss, reduced caloric intake and

increased exercise are associated with improvements in insulin resistance with a resulting improvement in blood glucose levels.⁶⁰⁻⁶³ Unfortunately, they are often the most difficult component to incorporate into a diabetes management program. Both dietary modification and exercise require the individual to make self-directed behaviour changes to help improve their overall diabetes management. This is often very difficult for patients to achieve. As with any lifestyle change, the key to successfully implementing a diet and exercise program is ensuring that the programs selected are individualized for each patient.^{3,58}

For the majority of individuals with type 2 diabetes, dietary modification, and physical exercise programs will not be sufficient for them to achieve their desired blood glucose levels. Approximately 90 percent of individuals with type 2 diabetes will require pharmacological treatment in the form of insulin or oral antihyperglycemic agents to achieve their blood glucose goals.⁶⁴ In addition to these agents, many individuals also receive various other pharmacological therapies to treat the various comorbid conditions or complications associated with type 2 diabetes.

The pharmacological treatment of type 2 diabetes has advanced considerably over the last several years. Prior to the mid 1990's, there were only two classes of oral agents to treat type 2 diabetes: insulin and sulfonylureas. Since 1995, however, several new novel classes of oral antihyperglycemic agents have been developed. In Canada, there are currently five oral pharmacological classes of agents used to treat hyperglycemia in type 2 diabetes: sulfonylureas, meglitinides, biguanides, thiazolidinediones, and alpha-glucosidase inhibitors.⁶⁵ Sulfonylureas (acetohexamide, chlorpropamide, glyburide, gliclazide and tolbutamide) are often termed 'hypoglycemic agents' because they have

the ability to lower blood glucose levels below normal levels. This is primarily achieved by increasing the release of insulin from the pancreas although they also increase the number of insulin receptors in peripheral tissue and reduce hepatic glucose production.⁶⁵ Meglitinides (repaglinide) are similar to sulfonylureas in that they stimulate insulin secretion from the pancreas. Unlike the sulfonylureas, however, the risk of hypoglycemia is diminished as the secretion of insulin decreases as glucose concentrations are lowered.⁶⁵ Biguanides (metformin) primarily decrease hepatic glucose production and may enhance insulin-stimulated glucose transport.⁶⁵ Thiazolidinediones (pioglitazone, rosiglitazone) enhance insulin action in hepatic and peripheral tissues, thus decreasing insulin resistance.⁶⁵ Alpha-glucosidase inhibitors (acarbose) inhibit enzymatic action within the small intestine resulting in decreased absorption of starches and sugars.⁶⁵

As with oral antihyperglycemic agents, insulin therapy has also advanced significantly. For individuals with type 2 diabetes who are unable to attain glycemic control with diet, exercise, and oral antihyperglycemic agents, insulin therapy is often required. Until recently, insulin products available in Canada could be classified into three categories according to their action profiles: short-acting, intermitted-acting, and long-acting insulin. Over the last several years, however, a new class of insulin analogues have become available; rapid-acting insulin. These new agents (insulin aspart and insulin lispro) have an onset of action within minutes following subcutaneous injection. There is also new long-acting insulin (insulin glargine). These new products have provided a wide range of agents available for individuals with diabetes to help control their blood glucose levels.⁶⁶ Until recently, the benefits of insulin therapy in type 2 diabetes were not well established. Recent data from two studies has helped to clarify this by demonstrating that

intensive insulin therapy reduces the risk of microvascular complications in individuals with type 2 diabetes^{59,67}

Pharmacological therapy in individuals with type 2 diabetes is extremely complicated and varies considerably depending upon the individual. The Canadian Diabetes Association recommends a stepwise approach to therapy. Initially, pharmacological therapy is reserved until a sufficient trial of lifestyle changes (dietary modification and physical exercise) fails to lower the individual's blood glucose levels to the desired goal or if symptoms of severe hyperglycemia persist.³ If pharmacological therapy is to be initiated, oral antihyperglycemic therapy should be initiated with a single agent.³

There have been numerous clinical trials completed evaluating the efficacy of the various antihyperglycemic agents when used as monotherapy. In general, when used as monotherapy, all agents have shown to have equal efficacy in reducing blood glucose levels with the exception of alpha-glucosidase inhibitors which are less effective.⁶⁸⁻⁷³ As a result, the initial choice of oral agent should be tailored to the individual depending upon their clinical circumstances.³ If monotherapy is not successful in achieving glycemic control after 2-4 months, progression to combination therapy is warranted. Generally, oral agents from other classes should be added until the desired blood glucose levels or maximum dose of each agent is achieved.³

Special consideration may be warranted in the use of metformin either alone or in combination with other oral agents. Metformin has been proven to be a highly effective agent in the treatment of type 2 diabetes.⁷⁰ In most cases, metformin has been used as a second-line agent either alone or in combination with other oral agents. In patients that

are obese, however, metformin monotherapy is now recommended as first line therapy.³ Metformin may be the preferred first line agent due to the results of a recent study which showed metformin monotherapy reduced all-cause related mortality compared with conventional therapy in obese individuals with type 2 diabetes.⁷⁴ Its role in the general type 2 diabetes population, however, is less certain. There is conflicting research as to the potential benefit of metformin therapy. In one study, the early addition of metformin therapy improved glycemic control in individuals who were on maximal sulfonylurea therapy yet still had suboptimal glycemic control.⁷⁵ Although glycemic control was improved, there was also an increase in the risk of diabetes-related mortality compared to sulfonylurea monotherapy.⁷⁴

There have also been several recent observational studies assessing mortality and metformin therapy with conflicting results.⁷⁶⁻⁷⁸ Fisman *et al.* reported that in individuals with type 2 diabetes and ischemic heart disease, metformin therapy, alone or in combination with sulfonylureas, resulted in a significant increased risk of all-cause related mortality. Similarly, Olsson *et al.* reported that in individuals with type 2 diabetes, combination therapy with metformin and sulfonylureas resulted in a significant increased risk of all-cause related mortality. Contrary to these studies, however, Johnson *et al.* reported that metformin, alone or in combination with sulfonylureas, was associated with reduced risk for all-cause and cardiovascular-related mortality compared to sulfonylurea monotherapy. The reason for the discrepancies between the studies is difficult to determine. It should be noted, however, with the early epidemiological studies conducted by Fisman *et al.* and Olsson *et al.*, the duration and severity of diabetes, as well as, adjustment for baseline cardiovascular risk was not completed and may have confounded

the results. In the study by Johnson *et al.*, these were controlled for in the analysis and may explain some of the differences observed compared to the previous studies. Due to the conflicting results, more research is needed to determine the impact of metformin therapy on mortality in patients with type 2 diabetes.

Most individuals with type 2 diabetes will respond to diet either alone or in combination with oral antihyperglycemic agents. Over time, however, individuals may become increasingly resistant to these therapies. As well, during times of stress or illness, diet and oral therapy may not be sufficient to maintain glycemic control. As a result, insulin therapy is recommended to achieve glycemic control. The type of insulin and doses should be individualized and may be used with or without oral agents.³

2.2 Complications of Type 2 Diabetes Mellitus

Although dietary modification, exercise, and pharmacological therapy have impacted enormously on the management of type 2 diabetes, it is still associated with significant long-term microvascular and macrovascular complications. Until the discovery of insulin in the 1920's, the long-term complications of diabetes were relatively unknown. Prior to the insulin era, diabetes was often a fatal condition which generally occurred shortly following clinical diagnosis of the disease.⁷⁹ Since the introduction of pharmacological therapy, however, long-term microvascular and macrovascular complications have caused the most morbidity and mortality in individuals with diabetes.⁸⁰

2.2.1 Microvascular Complications

Microvascular complications of diabetes include retinopathy, nephropathy, neuropathy and foot disorders. These complications result in a significant burden to both the individual and the health care system. A recent economic analysis on the costs for acute and chronic diabetes care indicated that the burden to the health care system associated with microvascular complications is approximately \$380 million (U.S. dollars).⁴ Many of these complications can be prevented or at least limited with proper medical management. Unfortunately, due to the silent onset and progression of type 2 diabetes, many individuals already have established microvascular disease at time of diagnosis rendering prevention impossible. In fact, according to the results of the UKPDS study, approximately 50 percent of individuals had complications of diabetes at baseline.³⁹

The burden to the individual associated with microvascular complications is substantial. Diabetic retinopathy is the leading cause of blindness in patients 20-74 years of age in North America and occurs in 33 percent of individuals with type 2 diabetes.³ Diabetes is also the leading cause of end-stage renal disease in Canada. Although less than 20 percent of individuals with type 2 diabetes will develop nephropathy, it is second only to cardiovascular disease in terms of diabetes complications associated with the greatest morbidity and mortality.^{3,81} Neuropathy also causes significant morbidity in patients with type 2 diabetes. Approximately 40-50 percent of individuals with type 2 diabetes will develop detectable neuropathy within 10 years of diabetes onset although many of these individuals are asymptomatic.³

The pathogenesis of long-term complications associated with diabetes has been intensely researched for the past several decades. Epidemiological studies have suggested that poor glycemic control was associated with increased microvascular complications in individuals with diabetes.⁸²⁻⁸⁴ Small, early clinical trials evaluating the potential benefits of intensive glucose control and the development of microvascular complications did not convincingly support this claim.⁸⁵⁻⁸⁷ The results of the Diabetes Control and Complications Trial (DCCT), however, has since shown that intensive glucose control significantly slows both the development and progression of retinopathy, nephropathy, and neuropathy in individuals with type 1 diabetes.⁴²

Until recently, the benefits of intensive glucose control and the development of microvascular complications in individuals with type 2 diabetes was less certain. Although some authors advocated tight glycemic control in individuals with type 2 diabetes to reduce microvascular complications, there was a lack of evidence to support these claims.^{88,89} A small, randomized control trial conducted by Ohkubo *et al.* provided some support for tight glycemic control in individuals with type 2 diabetes. They randomized 110 non-obese Japanese people with type 2 diabetes either to an intensive insulin regimen aimed at tight glycemic control or to conventional insulin therapy. After 6 years of follow-up, they concluded that intensive glycemic control with multiple insulin injection treatment significantly delayed the onset and the progression of diabetic retinopathy, nephropathy and neuropathy.⁵⁹ Unfortunately, due to the small selective sample size, it remained uncertain whether these benefits could be seen in other sub-populations (i.e., obese individuals) with type 2 diabetes. As well, it also still remained uncertain if tight glycemic control with oral antidiabetic agents could produce similar

results. These limitations have been addressed, however, by the United Kingdom Prospective Diabetes Study (UKPDS).

The UKPDS is the largest study in individuals with type 2 diabetes that has been completed to date. This large, multicentre study randomized 3867 newly diagnosed patients with type 2 diabetes to either intensive glucose control with either a sulphonylurea (chlorpropamide, glibenclamide, or glipizide), insulin or combination therapy or to conventional glycemic control with diet therapy. Individuals were followed prospectively for a 10-year period. At the conclusion of the study, the median haemoglobin A_{1c} (HbA_{1c}) was 7.0 percent and 7.9 percent for patients in the intensive glycemic control and conventional group, respectively. This resulted in a 25 percent risk reduction in microvascular endpoints for individuals assigned to the intensive glucose control group. Further analysis revealed that for every 1 percent absolute lowering of HbA_{1c}, there is a 35 percent reduction in microvascular complications. The UKPDS has provided support that maintenance of tight glycemic control in individuals with type 2 diabetes may be advantageous unless comorbid conditions warrant otherwise.^{3:58}

2.2.2 Macrovascular Complications

The development of type 2 diabetes is also associated with significant macrovascular complications. Macrovascular complications of type 2 diabetes are approaching epidemic proportions.⁹⁰ Macrovascular complications are the major contributor to direct and indirect costs of treating diabetes. In Canada, it has been estimated that the total cost associated with macrovascular complications in individuals with diabetes is approximately \$1.6 billion (U.S. dollars). This represents over 30 percent

of the total cost to treat diabetes in Canada.^{4,91} Macrovascular complications also have a significant negative impact on self-reported health-related quality of life in people with diabetes.⁹²

Macrovascular complications are the leading cause of morbidity and mortality in people with diabetes.^{93,94} Clinical and epidemiological evidence has indicated that 50 – 70 percent of all deaths in individuals with diabetes can be attributed to cardiovascular disease.^{9,14-16} Furthermore, individuals with type 2 diabetes appear to be at greater risk for cardiovascular-related mortality compared to individuals with type 1 diabetes or the general population.^{1,95} In general, the incidence of, and mortality from, cardiovascular disease is two to threefold higher for men and three to fourfold higher for women with diabetes as compared to the general nondiabetic population.⁵⁻⁸

In individuals with diabetes, atherosclerosis of the coronary arteries develops at an earlier age and occurs much more extensively and diffusely than in the general population.⁹⁰ The result is that the potential risk of myocardial infarction is substantially greater in individuals with diabetes. Individuals with diabetes without a previous myocardial infarction are at the same risk for an acute coronary event as individuals without diabetes who have had a previous myocardial infarction.⁹⁰ Evidence from a large population-based study has also suggested that individuals with diabetes, who have had a myocardial infarction, are more likely to have a reinfarction compared to individuals without diabetes.^{14,96}

Although most individuals with diabetes exhibit the usual signs and symptoms of coronary ischemia (e.g., chest pain, diaphoresis, anxiety), a large portion experience 'silent' coronary ischemia in which these symptoms are not present. These 'silent' attacks

also occur in the general nondiabetic population. In individuals with diabetes, however, silent ischemia and silent myocardial infarction are two to three times more common than the general population and increase with increasing duration of diabetes.¹⁰⁻¹²

Diabetes is also a poor prognostic factor for either early or late outcomes in acute coronary syndromes.⁹⁰ Individuals with diabetes experiencing unstable angina pectoris are at an increased risk of progressing to an acute myocardial infarction.⁹⁷ Individuals with diabetes are also at an increased risk of death following either fibrinolytic therapy or revascularization therapy for myocardial infarction compared with individuals without diabetes.^{16,98} Diabetes increases the risk of developing serious complications post myocardial infarction including increased rates of reinfarction, congestive heart failure and death.¹³ In fact, the 5 year mortality rate following an acute myocardial infarction may be as high as 50 percent for individuals with diabetes which is double compared to that of the general population.⁹⁰ The risk of mortality also appears to increase with increasing duration of diabetes, increasing age, and is more pronounced in women than in men.^{80,99}

Individuals with diabetes are also more prone to cerebrovascular disease. One study, which looked at predictors of stroke in the elderly, found that the frequency of diabetes was three times more compared to that of matched controls.¹⁰⁰ It has been estimated that the risk of stroke is somewhere between 150 – 400 percent higher for individuals with diabetes compared to the general population.^{101,102} As with coronary artery disease, cerebral vascular disease appears to develop at a much younger age in individuals with diabetes. Diabetes increases the risk of stroke in people under the age of 55 years by over ten-fold.^{101,103} Diabetes also affects outcomes following a stroke.

Individuals with diabetes are more likely to suffer from dementia, recurrence, and have higher rates of both all cause and stroke-related mortality.⁹⁰

Type 2 diabetes also significantly affects the peripheral vascular system. Diabetes increases the risk of peripheral artery disease by two to four-fold compared to the general population.⁹⁰ Individuals with diabetes also tend to develop more serious forms of peripheral artery disease compared to the general population. Individuals with diabetes are more prone to intermittent claudication and amputation.¹⁰⁴ It is estimated that individuals with diabetes have a fifteen to forty-fold increased risk for lower extremity amputations.¹⁰⁵

2.3.2 Cardiovascular Risk Reduction in Diabetes

As indicated above, the risk of cardiovascular disease is significantly higher in individuals with diabetes compared to the general population. Not surprisingly, due to the significant morbidity and mortality associated with the development of cardiovascular disease, there has been a greater emphasis placed on risk reduction. Although there have been significant declines in cardiovascular events in the general population, this has not been the case in individuals with diabetes. There has been no significant decline in the incidence of cardiovascular events in males with diabetes and in females the outcome has actually worsened over the years.¹⁰⁶

Numerous modifiable and non-modifiable risk factors for the development of cardiovascular disease have been identified. Non-modifiable risk factors include age, gender, race, genetics and duration of diabetes.¹⁰⁷ Increasing duration of diabetes, increasing age, and African-American descent are all strongly associated with the development of cardiovascular disease in individuals with diabetes.¹⁰⁷ Gender also has an

influence of cardiovascular risk in individuals with diabetes that is different from what is normally seen in the general population. In the general population, premenopausal women are at a lower risk for the development of cardiovascular disease compared to males without diabetes. In women with diabetes, however, this protective effect of female gender does not exist (i.e., the risk of cardiovascular disease in women with diabetes is equal to that of males with diabetes).¹⁰⁸

As in the general population, the three classic modifiable risk factors for cardiovascular disease are smoking, hypertension, and lipid level abnormalities.⁸ Studies have linked smoking with an increased risk in cardiovascular morbidity and mortality in individuals with diabetes.¹⁰⁹ Results from the MRFIT (Multiple Risk Factor Intervention Trial) have also indicated that the risk for cardiovascular events substantially increases with increasing blood pressure and cholesterol levels in individuals with diabetes. Furthermore, the risk for a cardiovascular event is significantly higher for individuals with diabetes compared to individuals without diabetes at any given measure of blood pressure or lipid level.¹¹⁰ In addition to these risk factors, obesity, decreased physical exercise and hyperinsulinemia are also modifiable risk factors that have been identified in both the development of diabetes and cardiovascular disease.^{111;112} These factors have not, however, been shown to be major risk factors for the development of cardiovascular disease in individuals with established type 2 diabetes.¹¹²

There is considerable research indicating that reductions in blood pressure can have a significant impact on morbidity and mortality in individuals with diabetes. There have been seven major clinical trials that have examined the impact of blood pressure control on cardiovascular outcomes in patients with type 2 diabetes.^{22;26;27;33;34;113;114} Only

the UKPDS, FACET (Fosinopril vs. Amlodipine Cardiovascular Events Trial) and ABCD (Appropriate Blood Pressure Control in Diabetes) trial, however, were specifically designed to study patients with type 2 diabetes.^{22,26,27} Other studies that have included patients with diabetes in subgroup analyses include the SHEP study (Systolic Hypertension in the Elderly Program), HOT study (Hypertension Optimal Treatment), Syst-Eur study (Systolic Hypertension in Europa), CAPPP study (Captopril Prevention Project) and STOP-2 study (Swedish Trial in Old Patients with Hypertension-2).^{33,34,113-115} Regardless of whether the studies included patients with diabetes as a primary study group or as a subgroup, reductions in either systolic blood pressure (SBP) or diastolic blood pressure (DBP) or both, have been shown to reduce the risk of various cardiovascular events although there may be differences in the effectiveness of the various antihypertensive therapies in this subpopulation.^{22,26,27,33,34,113-115}

Although there has not been a clinical trial on the effects of lipid-lowering therapy specifically in individuals with diabetes on cardiovascular outcomes, there is still strong evidence supporting the use of lipid therapy in this population. In the 4S (Scandinavian Simvastatin Survival Study) study, subjects with diabetes who did not receive simvastatin therapy had higher rates of cardiovascular events and total mortality (borderline significance) than subjects with diabetes who received therapy. These results strongly suggest that cholesterol lowering with simvastatin improves the prognosis of individuals with diabetes and established coronary heart disease (CHD).¹¹⁶ As well, in the CARE (Cholesterol And Recurrent Events) and VA-HIT (Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial) studies, pravastatin and gemfibrozil, respectively, significantly reduced the incidence of cardiovascular events in individuals

with diabetes.^{117;118} There is also evidence for the benefit of lipid-lowering therapy from the Helsinki Heart Study, LIPID (Long-Term Intervention with Pravastatin in Ischaemic Disease) and AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study) studies. In these studies, lipid-lowering therapy was associated with a reduction in cardiovascular events in subjects with diabetes although the results did not reach statistical significance.^{113;119-121}

Often overlooked in the management of individuals with diabetes is the use of acetylsalicylic acid (ASA) therapy. ASA therapy has been shown to reduce cardiovascular morbidity and mortality in patients with coronary artery disease and diabetes.¹²² ASA therapy (81 mg enteric coated tablet once daily) is recommended for primary prevention in all high risk individuals (i.e., over the age of 30 years) with diabetes and as secondary prevention in all individuals with coronary artery disease.³

Since diabetes is characterized by chronic hyperglycemia, it would seem reasonable that hyperglycemia could potentially be a modifiable risk factor for the development of cardiovascular disease. This concept has received considerable attention over the last few years. Observational studies have suggested that chronic hyperglycemia is associated with the development of cardiovascular disease in individuals with diabetes.^{93;112;123;123-125} In particular, the risk of myocardial infarction appears to increase with even slight increases in blood glucose levels above the normal range.¹²⁶

Unlike microvascular complications, there is currently little support that improvement in blood glucose levels leads to reductions in cardiovascular events or complications. There have been several randomized controlled trials assessing whether tight glycemic control improves macrovascular outcomes in patients with diabetes. The

first randomized trial was the University Group Diabetes Program (UGDP).¹²⁷ The results of the study indicated that there was no benefit of glycemic control in patients with new-onset type 2 diabetes on macrovascular disease. Furthermore, it was also reported that the oral hyperglycemic agents' used (tolbutamide and phenformin) were associated with an increase in cardiovascular mortality. A major criticism of the study, however, is that there were relatively few patients enrolled and the absolute difference in fasting plasma glucose between the treatments groups was extremely small. Contrary to this study, Ohkubo *et al.* reported that intensive glycemic control in Japanese individuals with type 2 diabetes was associated with reduced macrovascular risk.⁵⁹ As with the previous study, however, few patients were enrolled and the primary outcome of the study was to determine the impact of intensive glycemic control on microvascular outcomes not macrovascular outcomes.⁵⁹ Thus, the generalizability of these two studies is highly questionable.

These limitations have since been addressed with the recent results of the UKPDS. The UKPDS has indicated that tight glycemic control is associated with reductions in microvascular complications in patients with type 2 diabetes.³⁹ The impact on cardiovascular complications, however, was less favourable. Although a 16 percent reduction in the risk of combined fatal or non-fatal myocardial infarction and sudden death was observed in the UKPDS study, it did not reach statistical significance.³⁹ It is also important to note that there was no increase in cardiovascular events for individuals receiving sulfonylurea therapy as has been previously suggested by the UGDP.

Diabetes has been implicated as a major independent risk factor for the development of cardiovascular disease for many years, however, the basis for this

relationship has remained relatively unexplained.^{90,128} Many risk factors have been shown to be common to both diabetes and cardiovascular disease suggesting that diabetes and cardiovascular disease are part of the same continuum.⁹⁰ These observations have led to the 'common soil' hypothesis which suggests that both diabetes and cardiovascular disease share common genetic and environmental antecedents.¹²⁹

There is also increasing evidence from recent epidemiological and clinical trials suggesting that many individuals have pre-established cardiovascular disease prior to the onset of diabetes.^{40,130,131} In the San Antonio Heart Study, it was shown that subjects who developed diabetes had higher levels of cholesterol, triglycerides and blood pressure in the years preceding the diagnosis of diabetes.¹³⁰ A study by Hu *et al.* using data from the Nurses' Health Study showed similar results. The study prospectively followed over 100,000 women who were initially free of cardiovascular disease and diabetes at baseline. Subjects were followed for 20 years to determine the temporal relationship between the development of diabetes and cardiovascular disease. The authors concluded that the risk of developing cardiovascular disease was substantially elevated prior to any clinical diagnosis of diabetes.¹³¹

This, along with other research evidence, has provided strong support for the 'ticking clock' hypothesis which states that "the clock for coronary heart disease starts ticking before the onset of clinical diabetes".^{130,132} In one study involving patients with type 2 DM, 50 percent of patients had pre-established cardiovascular disease at the time of diagnosis of their diabetes.⁴⁰ It is due to this complex relationship between cardiovascular disease and diabetes that has many researchers looking for new novel risk factors associated with the development of diabetes and cardiovascular disease.

2.3.2.1 Novel Risk Factors

The conventional risk factors described above are commonly present in many individuals with type 2 diabetes.¹⁰⁶ It is also clear that the excess cardiovascular risk in individuals with type 2 diabetes can not be fully explained by these risk factors.¹⁰⁶ There have been several potential new novel risk factors that have been identified as being associated with the development of cardiovascular disease. Some of these factors are impaired fibrinolysis, abnormal platelet function, hypertriglyceridemia, low high density lipoproteins, increased insulin levels, increased homocysteine levels, and microalbuminuria.¹³³ In recent years, there has been considerable interest regarding the effects of the renin-angiotensin-aldosterone system (RAAS) on vascular endothelium and its role in the development of atherosclerosis and cardiovascular disease.

The RAAS is a complex system of vasoactive substances responsible for maintaining fluid, electrolyte and blood pressure homeostasis.¹³⁴ Early investigations into the RAAS perceived it to be primarily a neuroendocrine system. Recent research, however, has shown that a tissue specific RAAS also exists. This autocrine/paracrine tissue RAAS is believed to play a major role in the development of cardiovascular diseases.^{19-21;135}

The RAAS maintains cardiovascular homeostasis mainly through the actions of the angiotensin-converting-enzyme (ACE). ACE is a key component of both the circulating and tissue specific RAAS. Although ACE is located mainly in the membrane of the endothelium cells of the lung, it is also found in endothelial cells of arteries, capillaries and veins where it helps to regulate the vascular tone.¹³⁵ Renin secreted by the kidneys in response to changes in renal blood flow and pressure, converts

angiotensinogen from the liver to angiotensin I, a relatively inactive peptide. ACE then converts Angiotensin I to Angiotensin II, a potent vasoconstrictor, responsible for increasing blood pressure and stimulating the secretion of aldosterone.^{21,135}

There have been several epidemiological studies that have shown that a highly active RAAS is associated with an increased risk for myocardial infarction.^{136,137}

Alderman *et al.* reported that among 1,717 hypertensive subjects with high versus low renin profiles (a marker of RAAS activity), there was a 5 fold increase in the risk of myocardial infarction after controlling for other risk factors such as age, smoking status, cholesterol, blood glucose, and blood pressure.¹³⁶ Similarly, Blumenfeld *et al.* also found that in 349 subjects with suspected myocardial infarction, high plasma renin levels was a dominate independent risk factor for the development of an acute myocardial infarction.¹³⁷

Although the exact mechanism remains unclear, it is thought that the RAAS negatively affects that cardiovascular system mainly through the actions of ACE.¹³⁴ ACE appears to be a critical balancing enzyme between vasoconstriction/growth and vasodilation/growth inhibition within the vascular system. The negative vascular effects (i.e., vasoconstriction/growth) caused by ACE are largely due to the overproduction of angiotensin II. Angiotensin II induces hypertrophy and proliferation of vascular smooth muscle, stimulation of growth-promoting agents, and promotes super oxide radicals, all of which are key factors in the development of atherosclerosis.¹³⁸ It is not surprising given the potential critical role of ACE in the development of angiotensin II and subsequent atherosclerosis that there have been numerous trials evaluating the effects of angiotensin-converting enzyme inhibitors on cardiovascular morbidity and mortality.

2.3 Role of Angiotensin-Converting-Enzyme Inhibitors

The beneficial effects of ACE inhibitors were first established in the treatment of hypertension.¹³⁹ Since then, however, there have been numerous randomized controlled trials with ACE inhibitors in various cardiovascular diseases.^{19;23;30-36;115;138-166} Results of these studies suggest that ACE inhibitors can reduce cardiovascular morbidity and mortality in patients with established cardiovascular disease. The potential benefit of ACE inhibitors in specific subpopulations remains unclear. In particular, the potential benefits of ACE inhibitors on cardiovascular morbidity and mortality in patients with diabetes is less well studied.

2.3.1 Clinical Benefits of ACE Inhibitors in Diabetes Mellitus

Many of the cardiovascular trials mentioned above have included patients with diabetes; however, overall the number of patients studied has been relatively small. Furthermore, there have been very few studies with ACE inhibitors that have included patients with diabetes as a primary study group or as a subgroup for analysis (see Appendix B for a summary of the major clinical trials involving ACE inhibitors with diabetic subanalyses).^{22;23;25-29} There have only been six such studies conducted with ACE inhibitors in the treatment of hypertension.^{22;25-27;29;167} In the Appropriate Blood Pressure Control in Diabetes (ABCD) trial, the effects of moderate or intensive blood pressure control with either nisoldipine or enalapril was evaluated in 470 patients with type 2 diabetes. Both agents were equally effective in controlling blood pressure,

however, there was a lower incidence of fatal and non-fatal myocardial infarction in the patients treated with enalapril.²²

Similar results were observed in the Fosinopril versus Amlodipine Cardiovascular Events Randomized Trial (FACET).²⁶ Patients with hypertension and type 2 diabetes were randomly assigned to either fosinopril or amlodipine therapy. Although both agents were equally effective in lowering blood pressure, there was a statistically significant reduction in the combined endpoint of stroke, myocardial infarction, and angina requiring hospitalization and in the combined endpoint of fatal and non-fatal stroke or myocardial infarction. Unfortunately, the generalizability of both the ABCD and FACET study results are uncertain. In both studies, the effects on cardiovascular morbidity and mortality were only secondary endpoints of the studies. Thus, these studies may have not been sufficiently powered to address these questions.

ACE inhibitor therapy was also compared to calcium channel blockers in the Swedish Trial in Old Patients with Hypertension-2 (STOP-2) substudy in patients with diabetes.²⁹ Similar to the results of the FACET and ABCD study, although both agents reduced blood pressure equally, the use of ACE inhibitors was associated with a statistically significant reduction in myocardial infarction. There was no statistically significant difference, however, with regards to cardiovascular-related mortality, stroke or all cause-related mortality.²⁹

Although ACE inhibitors may be more beneficial than calcium channel blockers on cardiovascular morbidity and mortality in patients with diabetes, their beneficial effects compared to beta-blockers is less certain. The UKPDS 39 is the largest and longest randomized control trial in patients with type 2 diabetes that has been completed

to date. The primary purpose of the study was to compare the effect of intensive blood pressure control using captopril and atenolol on prevention of micro- and macrovascular complications in patients with type 2 diabetes. After a median follow-up of 8.4 years, both agents were equally effective in reducing complications associated with type 2 diabetes.²⁷

Contrary to these results, a subanalysis of the Captopril Prevention Project (CAPPP) suggests that ACE inhibitors may provide additional benefits over beta-blockers. The CAPPP study evaluated the effects of captopril verses conventional therapy (diuretics and/or beta-blockers) on cardiovascular morbidity and mortality in patients with hypertension. A subanalysis of the study showed that patients with diabetes who received captopril had a statistically significant reduction in the primary combined endpoint (fatal and non-fatal myocardial infarction, stroke, and other cardiovascular mortality) and in fatal and non-fatal myocardial infarction. There was also a statistically significant reduction in the secondary endpoints of all cause-related mortality and cardiovascular-related events in patients who received captopril compared to conventional therapy.²⁵

Although many of the previous studies evaluating the use of ACE inhibitors in hypertension have shown benefits in patients with diabetes, results from the recently completed Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) study contradict many of these studies.¹⁶⁷ The ALLHAT study is the largest hypertension study completed to date enrolling over 33,000 patients with approximately 36% of those having a diagnosis of type 2 DM. The study was designed to evaluate whether treatment with a calcium channel blocker (amlodipine) or an ACE inhibitor

(lisinopril) lowers the incidence of coronary heart disease or other cardiovascular disease events versus treatment with a diuretic (chlorthalidone). In a subgroup analysis of patients with type 2 DM, after a mean follow-up of 4.9 years, therapy with lisinopril was not significantly better than therapy with chlorthalidone with regards to the primary outcome of non-fatal myocardial infarction or fatal coronary heart disease (CHD), or secondary outcomes consisting of all cause-related mortality, stroke, combined coronary heart disease (non-fatal myocardial infarction or fatal CHD, coronary revascularization, hospitalized angina), and combined cardiovascular disease (combined CHD, stroke, other treated angina, heart failure, and peripheral vascular disease). However, because this was a subgroup analysis, it is possible the study was not sufficiently powered to detect a difference between the therapies.

ACE inhibitors have also been studied in patients with diabetes following acute myocardial infarction.^{23,28} In the GISSI-3 study, the effect of treatment with lisinopril, transdermal glycerol trinitrate, and their combination on survival and left ventricular function following an acute myocardial infarction was evaluated. At the end of 6 weeks of follow-up, patients with diabetes who received lisinopril showed a significant reduction in the primary endpoint of all cause-related mortality.²⁸ Similar results were seen in the Trandolopril Cardiac Evaluation (TRACE) study. Patients with diabetes who received trandolopril following an acute myocardial infarction showed a significant reduction in the primary endpoint of all cause-related mortality compared to placebo. There was also a significant reduction in the secondary endpoint of cardiovascular-related mortality, sudden death and progression to heart failure compared to placebo.²³

2.3.2 Prevention of Cardiovascular Morbidity & Mortality

Although there have been numerous randomized controlled trials with ACE inhibitors in various cardiovascular diseases, the effects of ACE inhibition on the prevention of cardiovascular morbidity and mortality have not been clearly established. Results of a meta-analysis in patients with low ejection fractions strongly suggested that a reduction in activity of the RAAS by ACE inhibitors could improve cardiovascular morbidity and mortality, independent of their effects on ejection fraction, blood pressure, concomitant medication use, diabetes status, and cause of heart disease.^{20,37} These results have not been readily accepted.³⁷ With the recent results of the Heart Outcomes Prevention Evaluation (HOPE) study, however, there seems to be considerable support for this hypothesis.

The HOPE study evaluated the effects of the ACE inhibitor, ramipril, in preventing cardiovascular morbidity and mortality in a high risk population. The primary outcome was a composite endpoint of cardiovascular-related mortality, myocardial infarction, or stroke. Each outcome was also analyzed separately. Secondary outcomes included all cause-related mortality, the need for revascularization, hospitalization for unstable angina or heart failure, and complications related to diabetes. A total of 9,297 high risk patients (55 years of age or older) who had a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes plus at least one other cardiovascular risk factor and were not known to have low ejection fraction or heart failure, were randomized to either ramipril or placebo therapy.

The HOPE study was terminated early after a median follow-up period of 4.5 years due to clear evidence of a beneficial effect of ramipril. Patients treated with

ramipril compared to placebo had a statistically significant reduction in the incidence of the primary composite endpoint of cardiovascular-related mortality, myocardial infarction, or stroke, as well as, for each outcome analyzed separately. Patients treated with ramipril also had a statistically significant reduction in the secondary outcomes of all cause-related mortality, the need for revascularization, and complications related to diabetes.³⁷

The effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes was also assessed in the MICRO-HOPE substudy.²⁴ Of the participants in the HOPE study, 3577 (38%) patients had diabetes and were included in the MICRO-HOPE substudy. Similar to the HOPE results, treatment with ramipril significantly reduced the incidence of the primary composite endpoint of cardiovascular-related mortality, myocardial infarction, or stroke, as well as, for each outcome analyzed separately in patients with diabetes. Ramipril therapy also significantly reduced the incidence of microvascular complications in patients with diabetes.²⁴

Although the results of the HOPE and MICRO-HOPE substudy provide strong evidence for the use of ACE inhibitors to reduce cardiovascular morbidity and mortality, the results should only be viewed as evidence for secondary prevention.^{24;37} In the HOPE study 79.5 percent in the ramipril group and 81.4 percent in the placebo group had a history of coronary artery disease at baseline. Furthermore, over 50 percent of patients had a history of myocardial infarction with approximately 10 percent having occurred a myocardial infarction within the preceding year prior to enrolment. In the MICRO-HOPE substudy, approximately 60 percent of the patients had previous coronary heart disease and only 33 percent and 29 percent of patients in the ramipril and placebo groups,

respectively, were free of cardiovascular disease at baseline. There was also a relatively high prevalence of stroke or transient ischemic attacks (TIAs) at baseline in both the HOPE study and MICRO-HOPE substudy. In the HOPE study, approximately 11 percent of patients had a previous history of stroke or TIAs at baseline, while in the MICRO-HOPE substudy, approximately 8 percent had a history of stroke or endarterectomy.^{24,37}

Results of the MICRO-HOPE substudy also suggest that ACE inhibitors may not be equally effective in reducing cardiovascular morbidity and mortality in all subsets of patients with diabetes. In particular, the relative risk reduction did not reach statistical significance in subgroups of patients with diabetes without microalbuminuria, with no cardiovascular disease, and in patients receiving insulin therapy. This is despite a relatively high number of patients within each subgroup (microalbuminuria (n=2,437); no cardiovascular disease (n=1,119); insulin therapy (n=1,852)). It also remains uncertain whether the benefits of ACE inhibitors can be applied to individuals with diabetes under the age of 55 years. Due to the inclusion criteria (i.e., 55 years of age or older), the average age in the MICRO-HOPE study was 65 years of age.²⁴ As a result, it remains relatively unclear whether ACE inhibitors can reduce cardiovascular morbidity and mortality in younger individuals with diabetes without pre-established cardiovascular disease.

2.4 Databases Available from Saskatchewan Health

Health services in Saskatchewan are coordinated through the provincial government's department of Saskatchewan Health. Saskatchewan Health, along with 12 district health boards, plan and deliver health services to the nearly 1 million residents of

Saskatchewan. Saskatchewan residents receive universal health insurance and no residents are excluded based on socioeconomic status.¹⁶⁸ Funding for the program is provided, in all or part, by the provincial government through provincial taxes. To allow tracking of health care funding and utilization within the province, large computerized database systems have been developed. As a result, an extensive amount of health care information has been collected over the years. Although the information has primarily been collected for administrative purposes, researchers have recognized the value of the system for pharmacoepidemiological research. Information available for Saskatchewan Health includes the registry of the eligible population, prescription drug data, hospital services data, the cancer registry, and vital statistics.¹⁶⁸ Only the databases pertinent to the current research will be discussed.

2.4.1 Health Insurance Registration File (HIRF)

The HIRF is a comprehensive registry that includes all residents that are eligible for coverage in the province. Since 1968, over 2 million individuals have been registered with the system.¹⁶⁸ Approximately 95% of the Saskatchewan population are eligible for provincial health coverage.¹⁶⁹ Individuals who are not covered by Saskatchewan Health include all individuals who receive federal health coverage. This includes members of the Royal Canadian Mounted Police (RCMP), Canadian Forces, and federal inmates. Registered Indians, although included in the databases, are specially identified within the HIRF. This is the result of special health care insurance that is received by registered Indians within the province.¹⁶⁸

All eligible registered beneficiaries in Saskatchewan receive a health care identification number. Prior to 1991, individuals may have received more than one identification number throughout their lifetime. This was because prior to 1991 individuals were assigned an eight digit registered beneficiary number (RBN). The first six numbers were used to identify the family unit while the last two numbers represented the individual family member. One of the problems, however, with the system was individuals may have received more than one RBN depending on their family and marriage status (i.e., 18 years of age, marriage or remarriage). The system did allow individual's data to be linked according to their RBN; however, the system was considerably more cumbersome to work with. In 1991, the RBN was updated with a new nine digit Health Services Number (HSN). The HSN is a unique identification number assigned to all eligible residents for their lifetime. Like the RBN, the HSN number is recorded whenever health care services are utilized and allows linking of the various databases within Saskatchewan Health.¹⁶⁸

The HIRF records demographic data on all eligible residents in the province. Data collected includes information on the individual's name, sex, marital status, and month and year of birth. Information on name and address changes, births, deaths, new residents, and departing residents are also collected and updated daily. The registry is continually verified and all transactions are checked for accuracy of the demographic data. All discrepancies are manually checked and corrected.¹⁶⁸

2.4.2 Saskatchewan Prescription Drug Plan

All Saskatchewan residents are eligible for coverage under the Saskatchewan Prescription Drug Plan (SPDP). Approximately 9% of the population, however, is excluded from drug coverage.¹⁶⁸ This segment of the population is mainly represented by the registered Indians who have their prescription drug costs coverage by a separate, Federal government agency. Due to the special identification of these individuals within the databases, they can be excluded from the research databases at the researchers' request.¹⁶⁸

As with most provinces in Canada, prescriptions eligible for reimbursement are listed on the provincial formulary. The Saskatchewan formulary is a comprehensive list of provincial reimbursed prescription drugs intended for outpatient use. Medications used within the hospital systems and non-prescription medications are generally not included. The formulary is updated semi-annually and currently includes over 2500 drug products. Clearly, not all drugs available in Canada are included on the formulary. Only those agents that have been identified as therapeutically effective and cost effective are included on the formulary.¹⁶⁸

The SPDP also includes a process by which non-formulary drugs may be covered. This is controlled through the Exception Drug Status (EDS) program. Under this program, physicians may request that an individual receive reimbursement for a particular drug. This system is generally employed for drugs that are used for rare medical conditions, exceptionally expensive agents, drugs not normally used outside of the hospital system, or in situations when the drugs listed on the formulary are contraindicated for a specific patient and a non-formulary drug is required.¹⁷⁰

The SPDP was the first plan in Canada to provide drug benefits, beginning in September 1, 1975.¹⁶⁸ Until mid 1987, consumers paid a fixed co-pay of prescription drug costs. This co-pay was applied towards the professional fee applied to prescription medications by pharmacies. The remaining balance was manually submitted by pharmacists for reimbursement by the provincial government. On July 1, 1987, this co-pay system was replaced by a family based deductible system. Consumers paid the full cost of prescription medications until the deductible amount was reached. After this deductible has been reached, the consumer is then reimbursed for a portion of the prescription costs.¹⁶⁸

Although drug data is available since 1975, the database is incomplete between the dates of July 1987 to December 1988.¹⁶⁸ In July 1987, with the introduction of the new family deductible system, the SPDP lost the ability to track individual drug use. This was not corrected until January 1, 1989 when points of service (POS) computer terminals, connected via telecommunication lines to a central database were introduced. Using the individual's HSN, all prescription data is submitted and recorded by Saskatchewan Health. The SPDP still currently utilizes the family deductible system, which is \$850 semi-annually for most families. Once the deductible has been reached, most families receive a reimbursement at the time of purchase of 30% of the prescription drug cost. The family deductible system varies depending on income level.

Since the SPDP records information according to HSN, this information can be linked to other databases. The SPDP records information on patient specific data (name, age, sex, and designation of specialty status (e.g., welfare recipient)), drug data ((AHFS class, DIN, Active Ingredient Number), generic and brand names, strength and dosage

form, manufacture of drug, date dispensed, and quantity dispensed), prescriber data (individual prescriber identification number), dispensing pharmacy data and cost data.¹⁶⁸

2.4.2 Hospital Services Data

As with the SPDP, all residents of Saskatchewan are eligible to receive hospital care insurance under the hospital care insurance program. Hospitals provide all medically necessary hospital services without charge to the individual. Data is collected from all acute care inpatient separations, day surgeries, long-term care separations on patients who occupy a bed in a general hospital, inpatient psychiatric separations on patients treated in general hospitals, active rehabilitation, and out-of province hospital separations for registered beneficiaries. A separation is defined as the discharge, transfer, or death of an inpatient.¹⁶⁸

The hospital separation system includes various categories of data including patient, diagnostic and treatment information, and other data. Patient data includes the individual's HSN, sex, month and year of birth. Standard diagnostic and procedure classification systems are used to categorize discharge diagnoses and procedures. Up to three discharge diagnoses using a four digit World Health Organization International Classification of Diseases, Ninth Revision (ICD-9) are used to classify discharge diagnoses. Procedures are classified using a four digit Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures (CCP). Other information recorded includes admission date, separation date, level of care codes, length of stay, admission and separation types, case mix group, resource intensity weights, attending physician or surgeon identification numbers, and hospital identification numbers. All of this data is

generally recorded at the hospital level with limited validation of the accuracy of the coding undertaken centrally by Saskatchewan Health. All hospital service data is compared with the HRIF for patient eligibility and for identification and demographic accuracy.¹⁶⁸

2.5 Summary

Type 2 diabetes mellitus is a complex disorder resulting from insulin resistance, relative insulin deficiency or both. Although there have been significant improvements in the pharmacological management of patients with type 2 diabetes, it is still associated with significant morbidity and mortality. In particular, patients with type 2 diabetes have a significantly increased risk of developing cardiovascular diseases including atherosclerosis, coronary artery disease, stroke, and peripheral vascular disease. It also appears that type 2 diabetes and cardiovascular disease share many common risk factors. Uncertainty remains as to the link between type 2 diabetes and cardiovascular disease. The occurrence of cardiovascular disease in individuals with diabetes may be the result of insulin resistance syndrome or other unknown factors.¹⁷¹ It is well known, however, that the classic risk factors associated with the development of cardiovascular disease cannot fully account for the high incidence of cardiovascular disease in individuals with type 2 diabetes. As a result, new novel risk factors, such as the RAAS, have been investigated regarding its potential role in the development of cardiovascular disease.

Numerous studies in cardiovascular disease have shown that the RAAS may be a key factor in the development of cardiovascular disease. Evidence from large-scale clinical trials also suggests that attenuation of the RAAS by ACE inhibitors may prevent

or delay the development of cardiovascular disease in certain subpopulations.

Unfortunately, the role of ACE inhibitors for the prevention of cardiovascular disease in individuals with type 2 diabetes is less certain. There have been relatively few studies that have included patients with diabetes as a primary study group or as a subgroup analysis. As well, most of the studies completed to date have investigated the use of ACE inhibitors for secondary prevention of cardiovascular events, not primary prevention. Although the HOPE study was designed to study the effects of the ACE inhibitor, ramipril, in high risk individuals, the results should only be interpreted as support for ACE inhibitor therapy for secondary prevention. Only 20% of individuals enrolled in the HOPE study were free of cardiovascular disease at baseline. Furthermore, subanalysis of the MICRO-HOPE study questions the ability of ACE inhibitors to prevent cardiovascular events in individuals without previous cardiovascular disease. Despite a relatively large subgroup, ramipril was not shown to be any more effective in preventing the development of cardiovascular disease than placebo in individuals without pre-established cardiovascular disease.²⁴ The role of ACE inhibitors for primary prevention remains uncertain.

There are also concerns whether or not the results of large-scale clinical trials can be applied in a 'real world' setting. All of the studies of ACE inhibitor use have used tight inclusion/exclusion criteria. The studies that have been completed have been very selective in the age categories of patients with diabetes who have been included in the studies. Since the effects of ACE inhibitors have not been studied in patients in all ages of type 2 diabetes, it is difficult to determine if the results can be applied to all patients. It also remains uncertain whether the benefits of ACE inhibitors can be applied to the

larger, less controlled, community setting where the majority of care is provided by general practitioners (GPs) and family physicians.

The computerized databases of Saskatchewan Health provided a unique dataset to study the effects of ACE inhibitors on cardiovascular morbidity and mortality from a 'real world' perspective. Computerized records were available to allow for continuous follow-up to identify clinical effects associated with ACE inhibitor use. Data available from Saskatchewan Health allowed characterization of drug use, hospitalizations, and clinical events and mortality. By using the Saskatchewan Health databases, many of the limitations associated with previous research was addressed. The Saskatchewan Health databases provided the opportunity to conduct a large, population based study evaluating the long-term use of ACE inhibitors for primary prevention of cardiovascular morbidity and mortality in patients of all ages with type 2 diabetes.

CHAPTER 3: METHODS

3.1 Definitions

The following terms are used in describing the methodology of the study:

Beneficiary: those registered residents of Saskatchewan who are eligible to receive SPDP benefits in the province. This excludes all members of Royal Canadian Mounted Police (RCMP), Canadian Forces, federal inmates, and registered Indians.

Cohort drug: ACE inhibitors (Appendix C)

Index Year: the year in which SPDP beneficiaries entered the study by receiving their first prescription for a cohort drug. This study selected subjects based on beneficiaries' records of the SPDP between the study index years of January 1, 1991 and December 31, 1999.

Cohort Index Date: the date of the first prescription for a cohort drug in an index year.

Exposure Period: determined by subtracting the index prescription date from the date of the last prescription during the follow-up period.

3.2 Study Cohort Selection

A retrospective cohort design using the computerized outpatient prescription database of Saskatchewan Health was employed to compare clinical outcomes associated with ACE inhibitor use in type 2 diabetes. Data was available for eligible beneficiaries between the years of January 1, 1989 and December 31, 1999.

3.2.1 Inclusion Criteria

Two study cohorts were identified from a population of new oral antidiabetic users: new users of ACE inhibitors and non ACE inhibitor users. Persons eligible for inclusion in any study cohort were those registered beneficiaries of the SPDP, aged 30 years or older at the time of the study index date and having continuous coverage in the provincial health plan for at least one year prior to the study index date.

This population of new antidiabetic users was identified as those eligible beneficiaries with a prescription claim for a sulfonylurea or metformin (Appendix A) between the index years of January 1, 1991 and December 31, 1996, and having no prescription claims for any antidiabetic agent for one year prior to their diabetes index date.

3.2.1.1 New ACE Inhibitor Users

New ACE inhibitor users were identified from the population of new antidiabetic users as those eligible beneficiaries with a prescription claim for an ACE inhibitor (Appendix C) between the index years of January 1, 1991 and December 31, 1999, having no prescription claims for any ACE inhibitor prior to the cohort index date, and no prescription claims for any ACE inhibitor prior to the study (i.e., antidiabetic agent) index date.

New ACE inhibitor users were classified into one of two cohorts based on previous cardiovascular disease status, based on all hospital separation claims prior to the study index date. Subjects who had a hospital separation history for any cardiovascular disease using ICD-9 codes (Appendix D) prior to the ACE inhibitor index date were

classified into the *secondary prevention cohort*. Subjects who did not have a hospital separation history for any cardiovascular disease based on ICD-9 codes prior to the ACE inhibitor index date were classified into the *ACE inhibitor cohort*. Only the ACE inhibitor cohort was included in this study.

3.2.1.2 Non ACE Inhibitor Users

A cohort of non ACE inhibitor users (control cohort) were identified from the population of new antidiabetic users as those eligible beneficiaries without a prescription claim for an ACE inhibitor between the index years of January 1, 1989 and December 31, 1999.

3.2.2 Exclusion Criteria

3.2.2.1 Minimum Exposure Period

The minimum exposure period to an ACE inhibitor agent was 365 days. Beneficiaries with an exposure to an ACE inhibitor agent of less than 365 days duration were excluded from all analyses.

3.2.2.2 Medication Utilization History

We excluded all subjects with a previous prescription claim for a product containing nitroglycerin or a loop diuretic (Appendix E). Subjects in the non ACE inhibitor cohort were excluded if a prescription claim for a product containing nitroglycerin or a loop diuretic occurred prior to their oral antidiabetic index date. Subjects in the ACE inhibitor cohort were excluded if a prescription claim for a product

containing nitroglycerin or a loop diuretic occurred prior to their ACE inhibitor index date. The use of nitrates has been shown to be a strong indicator for established coronary disease.^{172;173} Similarly, the use of loop diuretic therapy has been shown to be a strong indicator for a diagnosis of congestive heart failure.^{174;175}

3.2.2.3 History of Cardiovascular Disease

Excluded from the study cohorts were all subjects whom had a hospital separation history for any cardiovascular disease (Appendix D) based on ICD-9 codes for 3 years prior to their oral antidiabetic index date.

As stated earlier, subjects in the ACE inhibitor cohort were also excluded if they had a hospital separation for any cardiovascular disease occurring between their oral antidiabetic index date and their ACE inhibitor index date.

3.3 Outcome Measures

3.3.1 Identification and Classification of Clinical Events

Health services data for the non ACE inhibitor and ACE inhibitor cohorts were followed prospectively for identification and classification of clinical events from the study index date until death, departure from the province, or December 31, 1999. Four different outcomes were considered; 1) all cause-related mortality; 2) cardiovascular-related mortality; 3) non-fatal myocardial infarction (MI) or non-fatal stroke; 4) a combined endpoint consisting of cardiovascular-related death or non-fatal MI or non-fatal stroke.

3.3.1.1 Mortality

The primary outcome for this study was all cause-related mortality. Deaths were identified through the computerized vital statistics file of Saskatchewan Health. Coding for the underlying cause of death is done by a trained coder who evaluates the medical certificate of death and applies World Health Organization (WHO) standardized decision rules to determine the underlying code of death. Specific ICD-9 codes for cardiovascular-related mortality were also identified (Appendix D).

3.3.1.2 Non-Fatal Myocardial Infarction or Non-Fatal Stroke

Non-fatal hospital separations for myocardial infarction or stroke were identified according to underlying ICD-9 coding employed by Saskatchewan Health. Specific ICD-9 codes for myocardial infarction and stroke used in this study were ICD-9 codes 410 and 430 – 438 (Appendix D), respectively.

3.3.1.3 Combined Outcome – Fatal and Non-Fatal Cardiovascular Events

The combined endpoint of cardiovascular-related death or non-fatal hospital separations for MI or stroke was also identified. In individuals who experienced more than one event, only the time to first event was considered.

3.4 Adjustment for Comorbidities

For all eligible cohort members, an index of overall morbidity was included in the analysis. A previously validated index of comorbidity, the Chronic Disease Score (CDS), which has been developed for use with automated pharmacy administrative databases

was used.¹⁷⁶⁻¹⁷⁸ The CDS provides an indication of burden of concurrent comorbidities by identifying specific drug therapies during the follow-up period. A modified CDS was used in this analysis, which was updated to include a wider range of marker drugs than originally identified (Appendix F).⁷⁷ This modified CDS has previously been used with this dataset.⁷⁷ The CDS was included in the multivariate analysis as a covariate.^{179,180}

The use of other disease specific drug therapies (Appendix G) was also included as covariates in the multivariate analysis to indicate additional, specific comorbidities. In particular, use of nitroglycerin has been shown to be a strong predictor of cardiovascular-related events and mortality in this dataset, over and above the CDS.⁷⁷

3.5 Data Analysis

3.5.1 Data Preparation

In order to analyze the data with a standard statistical software package, the data provided by Saskatchewan Health was incorporated into a summary record for each eligible beneficiary. We used information from three separate data files: 1) subject file, 2) outpatient prescription claims file, and 3) hospital file.

The subject file contained information on the following variables: birth month, birth year, sex, study index date, study exit date, CDS, death flag, and cause of death (Appendix H).

The outpatient prescription claims file contained information on the following variables: date of prescription claim, prescription drug category (Appendix I), quantity claimed, drug strength, drug formulation, and speciality of prescribing physician (Appendix J).

The hospital file contained information on the following variables: admission date, separation date, length of stay, type of discharge (e.g., medical discharge, death, transfer to another facility, signed out against medical advice, etc.), primary diagnosis (ICD-9 coded), secondary diagnosis (ICD-9 coded), other diagnoses (ICD-9 coded), three procedure codes for procedures received while in the hospital and type of claim (Appendix K).

Within all files, each subject was coded by Saskatchewan Health with a unique case study ID number. Data from the three databases were incorporated into a summary record for each eligible beneficiary by linking the study ID number. Thus, a complete record of subject demographic information, outpatient prescription medication claims and hospital separations between the index years of January 1, 1989 and December 31, 1999 were available for all eligible subjects.

3.5.2 Statistical Analysis

All statistical analyses were performed using SPSS for Windows (version 11.0).

3.5.2.1 Descriptive Statistics

Demographic and clinical variables used to characterize the two cohorts under study were described as mean and standard deviation or proportion, as appropriate. These included age, sex, duration of diabetes, CDS, and utilization of drug therapies throughout the follow-up period known to affect cardiovascular outcomes (Appendix G). In addition, the number of subjects who experienced the clinical event of interest was determined for

each cohort. The characteristics of the two cohorts under study were compared with a t-test or chi-square test depending on the nature of the dependent variable.

3.5.2.2 Crude Odds Ratios

Crude odds ratio (OR) calculations were used to assess the association between ACE inhibitor therapy and morbidity and mortality in patients with type 2 diabetes. Crude ORs were conducted for all clinical event rates of interest to this study (i.e., all cause-related mortality, combined endpoint, cardiovascular-related mortality, non-fatal myocardial infarction/stroke) between study groups. Subjects not receiving ACE inhibitor therapy for the duration of the study period (i.e., non ACE inhibitor cohort) served as the comparison group for all OR calculations. Crude OR and 95% CI were calculated for all covariates of interest.

3.5.2.3 Survival Analysis – Time to Outcome Event

In addition to univariate OR calculations, the relationships between ACE inhibitor use and clinical event rates was assessed using Cox proportional hazards regression. The main effects were tested with a dummy variable representing subjects who are exposed to ACE inhibitors (ACE inhibitor cohort) and subjects who are not exposed to ACE inhibitors (non ACE inhibitor cohort).

Cox proportional hazards regression is a method for modeling time-to-event data, rather than simply whether an event occurs or not, in the presence of 'censored' cases while simultaneously controlling for multiple confounding factors (covariates). Age, sex, CDS, insulin therapy, and other drug therapies known to affect cardiovascular outcomes

(Appendix G) were included as covariates in all Cox proportional hazards regression models. The Cox proportional hazards assumption of constant hazard was checked for all variables. In addition, all potentially clinically important first order interactions were also assessed in the Cox proportional hazards model. No clinically important or plausible interactions were identified. As a result, no interactions were included in the final model. The general Cox proportional hazards regression model that was used in this study is as follows:

$$\ln[h(t)/h_0(t)] = \beta X(\text{group}) + \beta X(\text{age}) + \beta X(\text{sex}) + \beta X(\text{CDS}) + \beta X(\text{antiplatelet}) + \beta X(\text{antiarrhythmic}) + \beta X(\text{BB}) + \beta X(\text{CCB}) + \beta X(\text{diuretics}) + \beta X(\text{loops}) + \beta X(\text{lipid}) + \beta X(\text{nitrates}) + \beta X(\text{insulin}) + \beta X(\text{metformin})$$

where $h_0(t)$ is the baseline hazard at time t , representing the hazard for a person with the value of 0 for all the independent variables (i.e., a reference case from the non ACE inhibitor cohort).

Hazard ratios, which represent the RR for clinical event rates, were estimated using the β -coefficients for the study group using the following test-based method:

$$HR = e^{\beta_i}$$

This relationship expresses the drug-exposure hazard ratio after controlling for all other potential confounding variables in the Cox proportional hazards model. Furthermore, a two sided 95% confidence interval for the true hazard ratio were also calculated using the following formula:

$$95\% \text{ CI} = e^{(\beta_i \pm 1.96 \text{ se}(\beta_i))}$$

In addition, survival curves were also produced from the Cox proportional hazards regression models.

CHAPTER 4: RESULTS

4.1 Study Sample

4.1.1 Study Cohorts

A total of 12,272 new users of oral antidiabetic drugs were identified between January 1, 1991 and December 31, 1996 (Figure 1). Excluded from this population of new users of oral antidiabetic drugs were 1,757 (14.3%) subjects who had a history for cardiovascular disease in the 3 years prior to their oral antidiabetic drug index date. Of the 10,515 subjects remaining, 4,800 subjects were identified as having a prescription claim for an ACE inhibitor and 5,715 subjects were identified as having no prescription claim for an ACE inhibitor between the index years of January 1, 1991 and December 31, 1999.

Of the 4,800 subjects with a prescription claim for an ACE inhibitor, the following subjects were excluded: 1,113 subjects for insufficient exposure to ACE inhibitor therapy (i.e., less than 365 days duration), 1,559 subjects had a prescription claim for an ACE inhibitor prior to their oral antidiabetic drug index date, 222 subjects had a combination of insufficient exposure to ACE inhibitor therapy and had a prescription claim for an ACE inhibitor prior to their oral antidiabetic drug index date.

As a result, 1,906 new ACE inhibitor users were identified between January 1, 1991 and December 31, 1999, who met the inclusion criteria. Of these subjects, 350 subjects were classified into the secondary prevention cohort due to a hospital separation history for cardiovascular disease prior to their ACE inhibitor index date. The remaining 1,556 subjects were classified into the ACE inhibitor cohort.

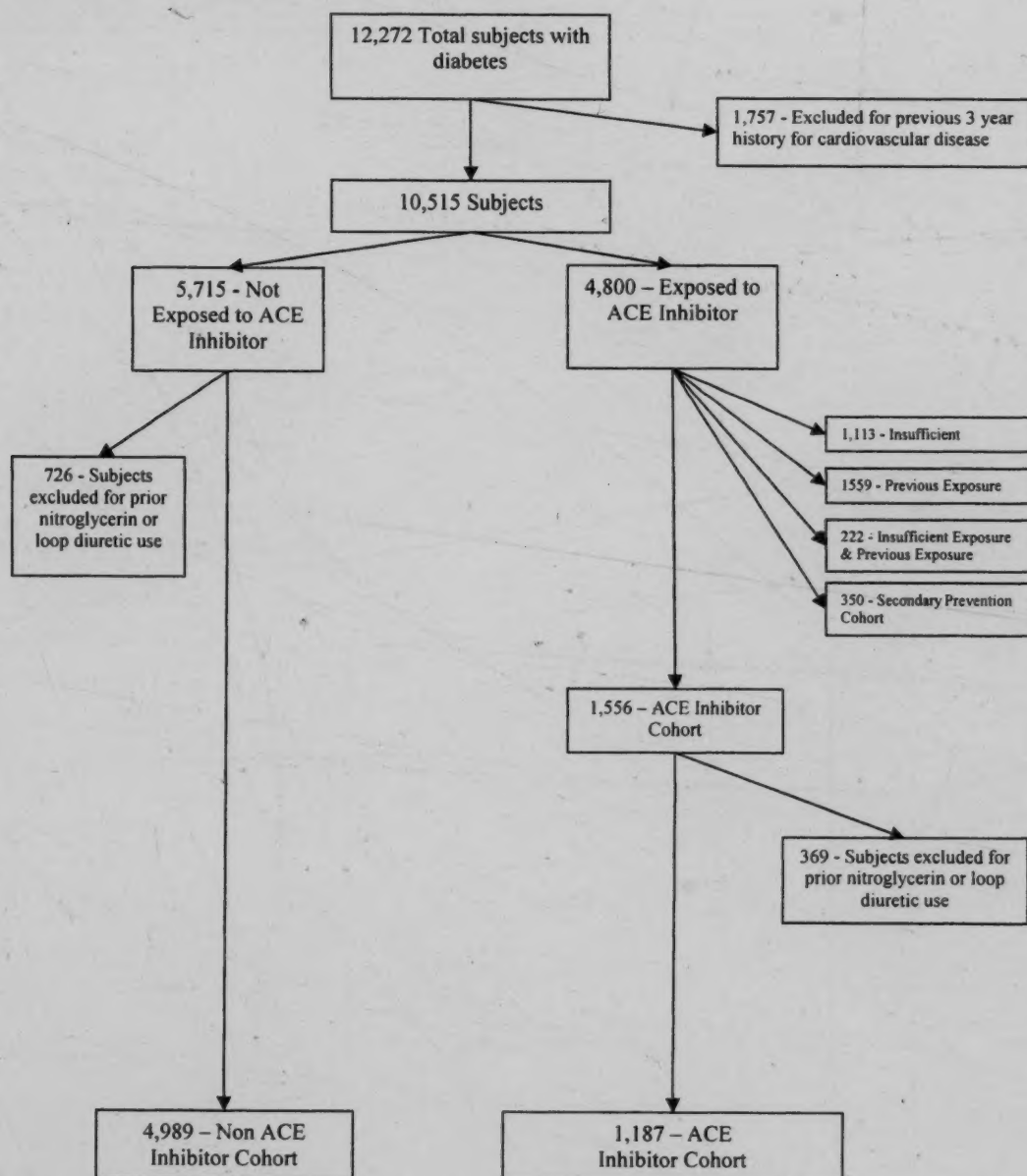
Excluded from the non ACE inhibitor and ACE inhibitor cohorts were all subjects with a previous prescription claim for a product containing nitroglycerin or a loop diuretic. Seven-hundred and twenty six and 369 subjects were excluded based on this criterion from the non ACE inhibitor and ACE inhibitor cohorts, respectively. Thus, 4,989 subjects in the non ACE inhibitor cohort and 1,187 subjects in the ACE inhibitor cohort were included in the analysis (Figure 1). The cohort characteristics are shown in Table 1.

Table 1. Characteristics for Non ACE Inhibitor and ACE Inhibitor Cohorts.

Characteristic	Non ACE Inhibitor Cohort (n=4,989)	ACE Inhibitor Cohort (n=1,187)	P Value
	No. (%) or Mean ± SD		
Age - yrs	60.9 ± 14.0	59.8 ± 12.2	0.013
Sex - male	2903 (58.2)	580 (48.9)	<0.001
Duration of Follow Up (yrs)	5.1 (2.2)	6.0 (1.7)	<0.001
Median	5.1	6.0	
Chronic Disease Score	5.8 ± 3.6	9.2 ± 3.0	<0.001
Median	5.0	9.0	

The mean (standard deviation (SD)) age for all subjects was 60.7 (SD 13.7) years and 56.4 percent were male. The entire cohort of 6,176 subjects was followed for a mean of 5.3 (SD 2.1) years, more than 32,000 patient-years. The mean CDS for the study groups was 6.4 (SD 3.7), with a median CDS of 6.0. Overall, the ACE inhibitor cohort was slightly younger (by about 1 year), contained fewer male subjects, had a longer duration of follow-up, and had a higher CDS score compared to the non ACE inhibitor cohort.

Figure 1. Summary of Study Cohort Selection.



4.1.2 Medication Utilization

Medications utilized throughout the duration of follow-up were significantly different between groups (Table 2).

Table 2. Medication Utilization Characteristics.

Medication*	Non ACE Inhibitor Cohort (n=4,989)	ACE Inhibitor Cohort (n=1,187)	P Value
	No. (%)		
Antiplatelet Therapy	475 (9.5)	180 (15.2)	<0.001
Antiarrhythmic Agent	271 (5.4)	96 (8.1)	0.001
Beta Blockers	560 (11.2)	310 (26.1)	<0.001
Calcium Channel Blockers	546 (10.9)	374 (31.5)	<0.001
Other Diuretics	344 (6.9)	356 (30.0)	<0.001
Loop Diuretics	561 (11.2)	207 (17.4)	<0.001
Lipid Lowering Therapy	617 (12.4)	267 (22.5)	<0.001
Nitroglycerin	428 (8.6)	142 (12.0)	<0.001
Metformin	2,752 (54.5)	862 (72.6)	<0.001
Insulin	586 (11.7)	157 (13.2)	0.159

* - Categories not mutually exclusive

There were significantly more subjects in the ACE inhibitor cohort who had prescription claims for various cardiovascular and diabetes related medications throughout the follow-up period. The use of insulin, however, was not statistically different between the two study groups. In addition, nitroglycerin which is a previously validated marker for cardiovascular disease, was dispensed for 570 (9.2%) of subjects during the follow-up period, with significantly more subjects receiving nitroglycerin in the ACE inhibitor cohort.

For subjects in the ACE inhibitor cohort, the mean length of time between their oral antidiabetic index date and initiation of ACE inhibitor therapy was 1.9 (SD 1.8)

years. The mean length of exposure to ACE inhibitor therapy was 3.6 (SD 1.9) years. The range of length of time exposed to ACE inhibitor therapy was from 1.0 to 8.8 years. Nine-hundred and twenty-eight (78.2%) subjects received ACE inhibitor therapy for at least 2 years duration.

4.2 All Cause-Related Mortality

4.2.1 Univariate Risk Estimates

A total of 955 (15.5%) deaths occurred during the follow-up period across both study cohorts. There were 853 (17.1%) deaths in the non ACE inhibitor cohort and 102 (8.6%) in the ACE inhibitor cohort ($p < 0.001$). The crude OR (95% CI) for all cause-related mortality was 0.46 (0.37 – 0.57) for the ACE inhibitor cohort compared to the non ACE inhibitor cohort. Crude ORs (95% CI) for the covariates for all cause-related mortality can be seen in Appendix L.1.

4.2.2 Survival Analysis – Time to All Cause-Related Mortality

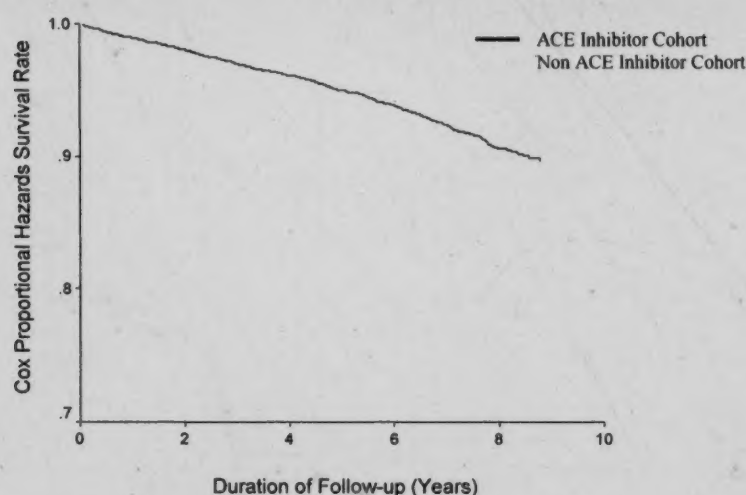
The unadjusted hazards ratio (HR) (95% CI) for all cause-related mortality from the Cox proportional hazards model was 0.43 (0.35 – 0.52). The adjusted HR (95% CI) for all cause-related mortality, after controlling for age, sex, CDS, and drug therapies known to affect cardiovascular outcomes, was 0.49 (0.40 – 0.61). A summary of the HRs (95% CI) for the various covariates used in the multivariate Cox proportional hazards model can be seen in Table 3.

Table 3. Adjusted Cox Proportional Hazards Ratio for All Cause-Related Mortality for the Non ACE Inhibitor and ACE Inhibitor Cohorts.

Covariates	Hazards Ratio (95% CI)
ACE Inhibitor Use	0.49 (0.40-0.61)
Sex - male	1.42 (1.25 – 1.62)
Age - >65 yr	4.11 (3.52 – 4.80)
CDS	1.01 (0.99 – 1.03)
Antiplatelet Agent Use	1.04 (0.87 – 1.25)
Antiarrhythmic Use	1.46 (1.20 – 1.78)
Beta Blocker Use	0.82 (0.66 – 1.01)
Calcium Channel Blocker Use	0.94 (0.77 – 1.13)
Diuretic Use (Except Loops)	0.93 (0.75 – 1.14)
Loop Diuretic Use	1.95 (1.64 – 2.31)
Lipid Lowering Therapy Use	0.55 (0.42 – 0.72)
Nitroglycerin Use	0.70 (0.55 – 0.89)
Metformin Use	0.59 (0.50 – 0.65)
Insulin Use	1.33 (1.09 – 1.61)

The adjusted Cox proportional hazards survival curves for all cause-related mortality for the ACE inhibitor and non ACE inhibitor cohorts can be seen in Figure 2. The survival curves separate shortly after initiation of ACE inhibitor therapy and continue to diverge throughout the follow-up period.

Figure 2. Adjusted Cox Proportional Hazards Survival Curves for All Cause-Related Mortality for the Non ACE Inhibitor and ACE Inhibitor Cohorts.



4.3 Fatal and Non-Fatal Cardiovascular Events

4.3.1 Univariate Risk Estimates

The combined endpoint (cardiovascular-related mortality, non-fatal myocardial infarction, and non-fatal stroke) occurred in 603 (9.8%) subjects during the follow-up period. The combined endpoint occurred in 483 (9.7%) and 120 (10.1%) of subjects in the non ACE inhibitor cohort and ACE inhibitor cohort, respectively ($p = 0.655$). The crude OR (95% CI) for the combined endpoint was 1.05 (0.85 – 1.30) for the ACE inhibitor cohort compared to the non ACE inhibitor cohort. Crude ORs (95% CI) for the covariates for the combined endpoint can be seen in Appendix L.2.

4.3.2 Survival Analysis – Time to Fatal and Non-Fatal Cardiovascular Events

The unadjusted HR (95% CI) for the combined endpoint from the Cox proportional hazards model was 0.89 (0.73 – 1.08). The adjusted HR (95% CI) for the

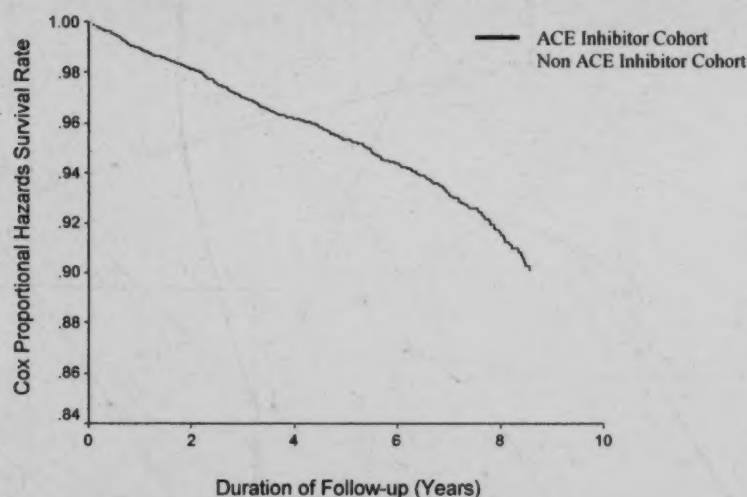
combined endpoint, after controlling for age, sex, CDS, and drug therapies known to affect cardiovascular outcomes, was 0.77 (0.62 – 0.96). A summary of the HRs (95% CI) for the various covariates used in the multivariate Cox proportional hazards model can be seen in Table 4.

Table 4. Adjusted Cox Proportional Hazards Ratio for the Combined Endpoint for the Non ACE Inhibitor and ACE Inhibitor Cohorts.

Covariates	Hazards Ratio (95% CI)
ACE Inhibitor Use	0.77 (0.62 – 0.96)
Sex - male	1.58 (1.34 – 1.87)
Age - >65 yr	3.19 (2.64 – 3.85)
CDS	1.01 (0.98 – 1.04)
Antiplatelet Agent Use	2.76 (2.30 – 3.31)
Antiarrhythmic Use	1.27 (1.00 – 1.62)
Beta Blocker Use	1.39 (1.14 – 1.69)
Calcium Channel Blocker Use	1.32 (1.08 – 1.61)
Diuretic Use (Except Loops)	1.05 (0.83 – 1.32)
Loop Diuretic Use	1.26 (1.01 – 1.56)
Lipid Lowering Therapy Use	0.95 (0.75 – 1.21)
Nitroglycerin Use	1.69 (1.36 – 2.10)
Metformin Use	0.69 (0.58 – 0.81)
Insulin Use	1.06 (0.82 – 1.38)

The adjusted Cox proportional hazards survival curves for the combined endpoint for the ACE inhibitor and non ACE inhibitor cohorts can be seen in Figure 3. The survival curves separate shortly after initiation of ACE inhibitor therapy and continue to diverge throughout the follow-up period. The separation is not as large as the all cause-related mortality curves, however.

Figure 3. Adjusted Cox Proportional Hazards Survival Curves for the Combined Endpoint for the Non ACE Inhibitor and ACE Inhibitor Cohorts.



4.4 Cardiovascular-Related Mortality

4.4.1 Univariate Risk Estimates

A total of 301 (4.9%) cardiovascular-related deaths occurred during the follow-up period. There were 261 (5.2%) cardiovascular-related deaths in the non ACE inhibitor cohort and 40 (3.4%) in the ACE inhibitor cohort ($p = 0.007$). The crude OR (95% CI) for cardiovascular-related mortality was 0.63 (0.45 – 0.89) for the ACE inhibitor cohort

compared to the non ACE inhibitor cohort. Crude ORs (95% CI) for the covariates for the cardiovascular-related mortality can be seen in Appendix L.3.

4.4.2 Survival Analysis – Time to Cardiovascular-Related Mortality

The unadjusted HR (95% CI) for cardiovascular-related mortality from the Cox proportional hazards model was 0.54 (0.39 – 0.76). The adjusted HR (95% CI) for cardiovascular-related mortality, after controlling for age, sex, CDS, and drug therapies known to affect cardiovascular outcomes was 0.63 (0.44 – 0.90) (Table 5).

The adjusted Cox proportional hazards survival curves for all cardiovascular-related mortality for the ACE inhibitor and non ACE inhibitor cohorts can be seen in Figure 4. The survival curves separate shortly after initiation of ACE inhibitor therapy and continue to diverge throughout the follow-up period.

Figure 4. Adjusted Cox Proportional Hazards Survival Curves for Cardiovascular-Related Mortality for the Non ACE Inhibitor and ACE Inhibitor Cohorts.

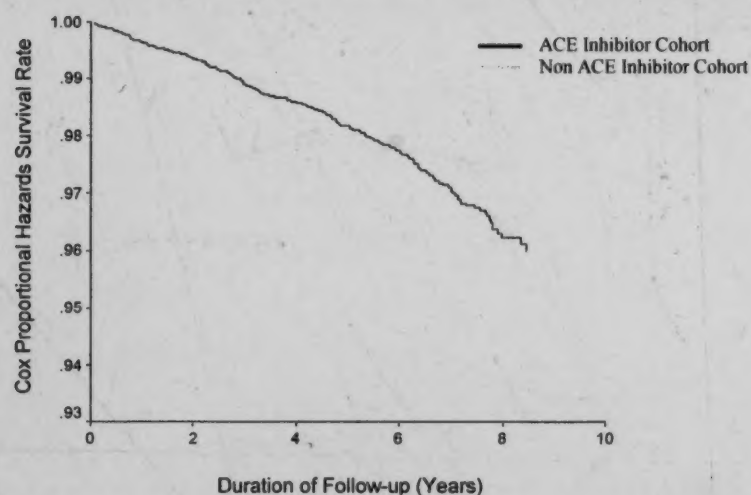


Table 5. Adjusted Cox Proportional Hazards Ratio for Cardiovascular-Related Mortality for the Non ACE Inhibitor and ACE Inhibitor Cohorts.

Covariates	Hazards Ratio (95% CI)
ACE Inhibitor Use	0.63 (0.44 – 0.90)
Sex - male	1.47 (1.26 – 1.86)
Age - >65 yr	4.78 (3.58 – 6.37)
CDS	0.98 (0.94 – 1.01)
Antiplatelet Agent Use	1.23 (1.28 – 2.50)
Antiarrhythmic Use	1.79 (1.28 -2.50)
Beta Blocker Use	0.96 (0.68 – 1.35)
Calcium Channel Blocker Use	1.16 (0.84 – 1.60)
Diuretic Use (Except Loops)	0.90 (0.62 – 1.29)
Loop Diuretic Use	1.95 (1.43 – 2.67)
Lipid Lowering Therapy Use	0.58 (0.36 – 0.93)
Nitroglycerin Use	0.77 (0.51 – 1.14)
Metformin Use	0.60 (0.48 – 0.76)
Insulin Use	0.82 (0.54 – 1.24)

4.5 Non-Fatal Myocardial Infarction or Non-Fatal Stroke

4.5.1 Univariate Risk Estimates

A total of 359 (5.8%) subjects had a non-fatal myocardial infarction or a non-fatal stroke during the follow-up period. There were 269 (5.4%) subjects in the non ACE inhibitor cohort and 90 (7.6%) in the ACE inhibitor cohort with a non-fatal myocardial

infarction or non-fatal stroke ($p = 0.004$). The crude OR (95% CI) for non-fatal myocardial infarction or non-fatal stroke was 1.44 (1.12 – 1.84) for the ACE inhibitor cohort compared to the non ACE inhibitor cohort. Crude ORs (95% CI) for the covariates for the non-fatal myocardial infarction or non-fatal stroke can be seen in Appendix L.4.

4.5.2 Survival Analysis – Time to Non-Fatal Myocardial Infarction or Non-Fatal Stroke.

The unadjusted HR (95% CI) for non-fatal myocardial infarction or non-fatal stroke from the Cox proportional hazards model was 1.20 (0.94 – 1.52). The adjusted HR (95% CI) for non-fatal myocardial infarction or non-fatal stroke was 0.85 (0.65 – 1.11) (Table 6). The adjusted Cox proportional hazards survival curves for non-fatal myocardial infarction or non-fatal stroke for the ACE inhibitor and non ACE inhibitor cohorts can be seen in Figure 5.

Figure 5. Adjusted Cox Proportional Hazards Survival Curves for Non-Fatal Myocardial Infarction or Non-Fatal Stroke for the Non ACE Inhibitor and ACE Inhibitor Cohorts.

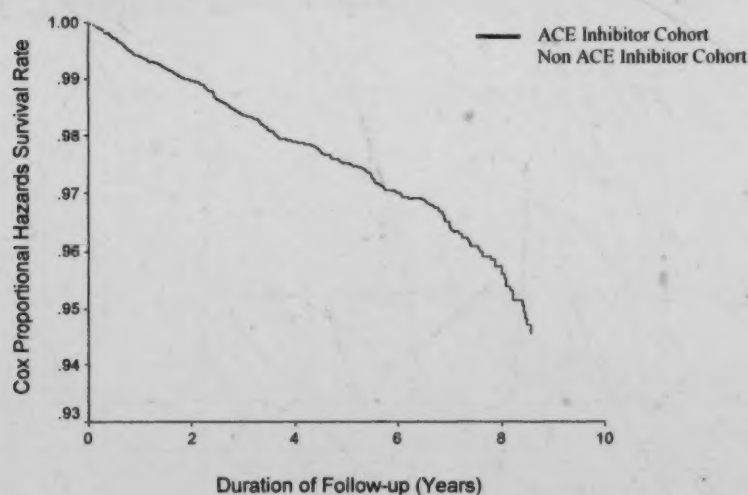


Table 6. Adjusted Cox Proportional Hazards Ratio for Non-Fatal Myocardial Infarction or Non-Fatal Stroke for the Non ACE Inhibitor and ACE Inhibitor Cohorts.

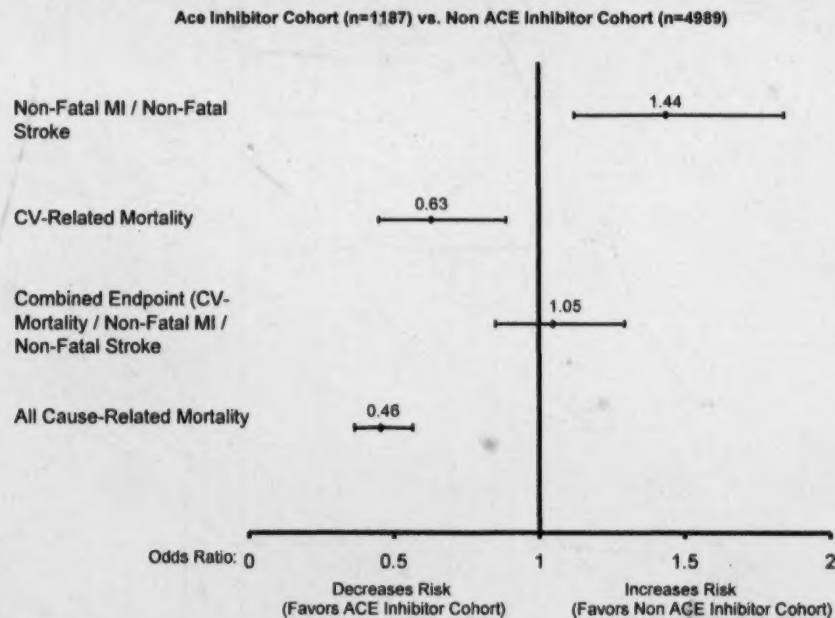
Covariates	Hazards Ratio (95% CI)
ACE Inhibitor Use	0.85 (0.65 – 1.11)
Sex - male	1.59 (1.28 – 1.99)
Age - >65 yr	2.46 (1.94 – 3.12)
CDS	1.04 (1.00 – 1.07)
Antiplatelet Agent Use	4.20 (3.33 – 5.29)
Antiarrhythmic Use	1.32 (0.98 – 1.77)
Beta Blocker Use	1.67 (1.32 – 2.11)
Calcium Channel Blocker Use	1.35 (1.06 – 1.73)
Diuretic Use (Except Loops)	1.13 (0.85 – 1.49)
Loop Diuretic Use	0.91 (0.69 – 1.21)
Lipid Lowering Therapy Use	1.10 (0.84 – 1.44)
Nitroglycerin Use	2.40 (1.85 – 3.11)
Metformin Use	0.80 (0.64 – 0.99)
Insulin Use	1.18 (0.87 – 1.61)

4.6 Summary

4.6.1 Crude Odds Ratios

Crude ORs calculations indicate that the use of ACE inhibitors was associated with a significant reduction in all cause-related mortality and cardiovascular-related mortality. There was no significant difference in the combined endpoint between study groups. Crude OR for non-fatal myocardial infarction and non-fatal stroke indicated that individuals receiving ACE inhibitors were at a significantly greater risk for these events compared to the non ACE inhibitor cohort. A summary of the crude OR (95% CI) can be seen in Figure 6.

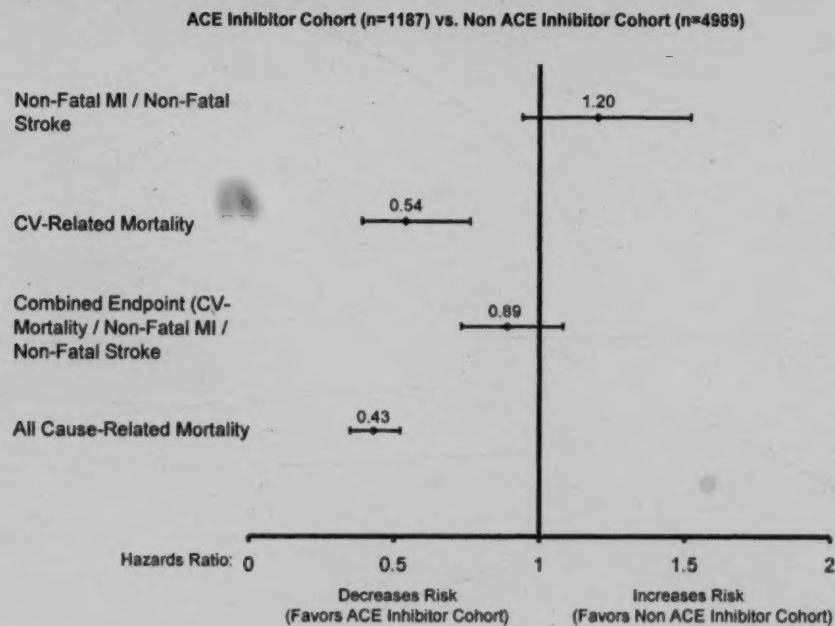
Figure 6. Crude Odds Ratios (95% CI) for Clinical Outcomes for the ACE Inhibitor Cohort Compared to the Non ACE Inhibitor Cohort.



4.6.2 Crude Hazard Ratios

The unadjusted HRs indicates that the use of ACE inhibitors was associated with a significant reduction in all cause-related mortality and cardiovascular-related mortality. There was no significant difference in the combined endpoint and in non-fatal myocardial infarction or non-fatal stroke between study groups. A summary of the unadjusted HRs (95% CI) can be seen in Figure 7.

Figure 7. Unadjusted Hazard Ratios (95% CI) for Clinical Outcomes for the ACE Inhibitor Cohort Compared to the Non ACE Inhibitor Cohort.

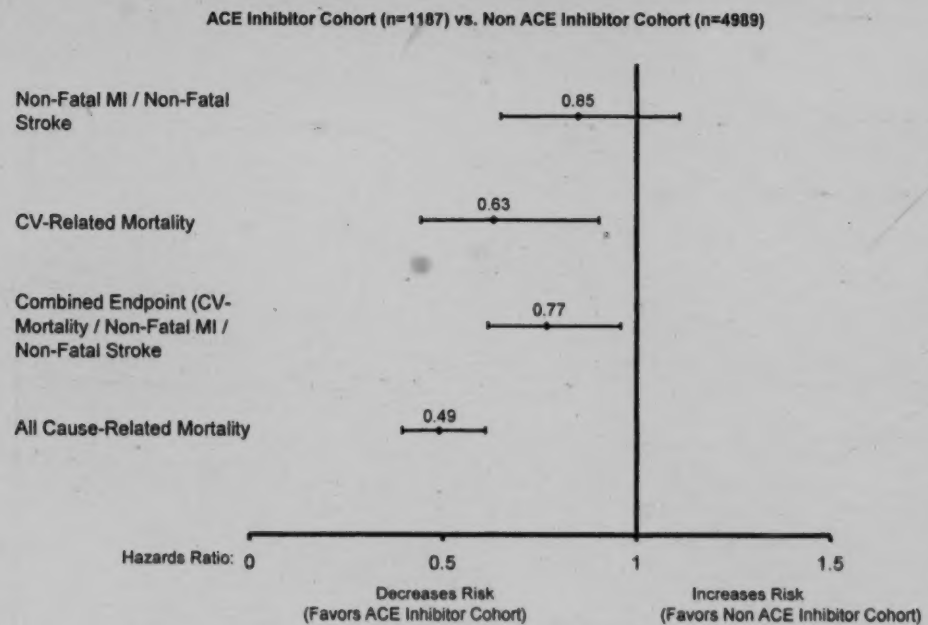


4.6.3 Adjusted Hazard Ratios

The results of the adjusted HRs were significantly different from those observed with the unadjusted HRs. After controlling for age, sex, CDS, and drug therapies known to affect cardiovascular outcomes, the use of ACE inhibitors was associated with a significant reduction in all cause-related mortality, cardiovascular-related mortality and in

the combined endpoint. In terms of non-fatal myocardial infarction and non-fatal stroke, ACE inhibitor use was also associated with reduced risk although this did not reach statistical significance. A summary of the adjusted HR (95% CI) can be seen in Figure 8.

Figure 8. Adjusted Hazard Ratios (95% CI) for Clinical Outcomes for the ACE Inhibitor Cohort Compared to the Non ACE Inhibitor Cohort.



CHAPTER 5: DISCUSSION

5.1 Summary and Discussion of Results

Type 2 diabetes mellitus (DM) affects over 90 percent of all individuals with DM and results in significant short and long term complications of the disease.³

Macrovascular complications are the leading causes of morbidity and mortality in people with type 2 DM. The incidence of hypertension, stroke, congestive heart disease, fatal arrhythmias, coronary heart disease, and myocardial infarction are significantly higher in individuals with diabetes as compared to the general population.⁵⁻¹⁶ Although significant advances in the understanding of the pathophysiology and management of diabetes have occurred over the last decade, macrovascular complications associated with the disease have not been significantly reduced and may be increasing in certain patient populations.^{17,18}

Due to the high incidence of macrovascular complications in people with diabetes, there have been greater efforts aimed at risk reduction. In particular, the use of ACE inhibitor therapy on cardiovascular morbidity and mortality in patients with diabetes has been evaluated. Several studies, including the HOPE study, have suggested that ACE inhibitor therapy may reduce cardiovascular morbidity and mortality in patients with diabetes. Unfortunately, all of these studies have been highly controlled, randomized trials and have enrolled relatively few patients with diabetes. These studies have not addressed the use of ACE inhibitor therapy for primary prevention of cardiovascular disease in a 'real world' population of individuals with type 2 diabetes.

This retrospective cohort study was intended to build on previous research by evaluating the use of ACE inhibitors for primary prevention in a large, population based

study. After discussing the results from the present investigation and relating these findings to past research, the limitations of the present investigation will be discussed. Finally, implications of the findings to clinical practice and future research will be presented.

5.1.1 Morbidity and Mortality Outcome Measurements

Results from the present investigation indicated that in patients with type 2 DM ACE inhibitor therapy for primary prevention was associated with a statistically significant reduction in all cause-related mortality, and fatal and non-fatal cardiovascular events (i.e., cardiovascular-related mortality, non-fatal myocardial infarction or non-fatal stroke). Patients who received ACE inhibitors had a 51% reduction in overall mortality and 23%, and 37% relative risk reduction in all cardiovascular events or cardiovascular death, respectively. ACE inhibitor therapy was also associated with a 15% relative risk reduction in non-fatal myocardial infarction or non-fatal stroke; however, this was not statistically significant.

The results observed in the present investigation are consistent with results observed in other trials evaluating ACE inhibitors in people with diabetes. Direct comparison, however, with other trials is difficult and can only be made from a general point of view due to different study methods, comparative treatments under study, patient populations, and clinical outcomes assessed.

In six major clinical trials or sub-analyses evaluating the use of ACE inhibitors in patients with diabetes and hypertension, the effect of ACE inhibitor therapy on morbidity and mortality have been relatively consistent with results observed in the present

investigation. In the ABCD trial comparing enalapril and nisoldipine, enalapril was associated with risk reductions in the secondary endpoints of all cause-related mortality and cardiovascular-related mortality; however, these reductions were not statistically significant.¹⁸¹ A direct comparison of non-fatal myocardial infarction or non-fatal stroke observed in the present investigation cannot be made with results of the ABCD study as these outcomes were analyzed separately and in combination with fatal events. In the ABCD study, there was a statistically significant risk reduction in non-fatal and fatal myocardial infarction, but no statistically significant difference in cerebrovascular events between groups, although there was a trend towards better outcomes in the enalapril group. In the present investigation, there was a trend towards reduced risk for non-fatal myocardial infarction or non-fatal stroke; however, this did not reach statistical significance.

Similar results to those observed in the present investigation were seen in the UKPDS 39 study comparing captopril versus atenolol.²⁷ After 9 years of follow-up, captopril therapy was associated with a reduced risk of all cause-related mortality and cardiovascular-related mortality; however, there was no statistically significant difference between captopril and atenolol therapy. It should be noted that there is still considerable debate as to whether the UKPDS 39 study was appropriately designed to detect differences between the study groups.¹⁸² In the present investigation, ACE inhibitor therapy was not compared to a specific active therapy on cardiovascular outcomes. As a result, direct comparisons between the two studies is difficult although both support reduced mortality rates with the use of ACE inhibitor therapy.

The results of the CAPPP substudy also provide support for lower morbidity and mortality rates in patients with diabetes receiving ACE inhibitor therapy. In the CAPPP substudy, 717 patients with diabetes were randomized to either captopril or conventional therapy (diuretics and/or beta-blockers). After 6.1 years of follow-up, patients assigned to captopril therapy had a 46% and 41% relative risk reduction in all cause-related mortality and in the combined endpoint of fatal and non-fatal myocardial infarction, stroke and other CV mortality, respectively.²⁵ These results are similar to the results observed in the present investigation, which showed a 51% and 23% relative risk reduction in these endpoints, respectively. There was also a 66% and 33% relative risk reduction in fatal and non-fatal myocardial infarction and all cardiovascular events combined, respectively, for patients assigned to receive captopril in the CAPPP substudy. Cardiovascular-related mortality was also reduced in the ACE inhibitor treated patients although there was no significant difference between the two groups.

The results of the FACET trial are also consistent with results observed in present investigation. After 3.5 years of follow-up, fosinopril compared to amlodipine therapy was associated with a 51% relative risk reduction in the combined endpoint of stroke, myocardial infarction or angina requiring hospitalization. There was also a significant 42% relative risk reduction in non-fatal and fatal stroke and non-fatal and fatal myocardial infarction.²⁶ In the present investigation, there was not a statistically significant risk reduction in non-fatal myocardial infarction or non-fatal stroke. No comparisons can be made with the results of the FACET trial with respect to all cause-related mortality or cardiovascular-related mortality as these were not clinical endpoints assessed in that study.

Results of a subanalysis of the STOP Hypertension 2 study group are not consistent with our results.²⁹ The subanalysis had 719 elderly diabetic patients with diabetes who were randomly assigned to therapy with conventional agents (i.e., diuretics and/or beta-blockers), calcium channel blockers or ACE inhibitors. Results of the study indicated that ACE inhibitors were not significantly better than conventional therapy on cardiovascular outcomes. In addition, there was no observed benefit of ACE inhibitors with regards to all cause mortality compared to conventional therapy. Comparison with individuals receiving calcium channel blockers indicated similar results although there was a statistically significant reduction in myocardial infarction in favour of the ACE inhibitor cohort.²⁹ It should be noted, however, that in the STOP Hypertension 2 study only elderly individuals were included in the study and may not be comparable to the population studied in the our investigation.

Recent results of the ALLHAT study are similar to those observed in the STOP Hypertension 2 subanalysis, which seem to contradict many of the previous studies completed to date with ACE inhibitors.¹⁶⁷ The ALLHAT study was a large randomized control trial to determine whether treatment with a calcium channel blocker (amlodipine) or an ACE inhibitor (lisonopril) lowers the incidence of coronary heart disease or other cardiovascular disease in patients with hypertension compared to treatment with a diuretic (chlorthalidone). As with many previous ACE inhibitor studies, this was a secondary prevention trial as over 50% of patients enrolled had a history of cardiovascular disease. Patients with type 2 DM were included in the study and represented approximately 36% of the total study population. Subgroup analysis of the patients with diabetes indicated that in comparison to chlorthalidone, therapy with

lisinopril was not statistically better with regards to non-fatal myocardial infarction plus fatal coronary heart disease, all cause-related mortality, stroke, combined coronary heart disease, and combined cardiovascular disease. Furthermore, therapy with chlorthalidone was observed to be significantly better than lisinopril with regards to heart failure. These results are not consistent with those observed in the present investigation. In the present investigation, a reduction in all cause-related mortality, cardiovascular-related death and in the combined fatal and non-fatal events was observed. The reason for the discrepancies in the results is not known, however, it should be noted that our study was not designed as a hypertension study.

Of the studies completed to date, the HOPE study provides the best comparison and most closely resembles the patient population and outcomes of interest evaluated in our investigation. In the HOPE study, the effects of the ACE inhibitor, ramipril, in preventing cardiovascular morbidity and mortality was evaluated. A total of 9,297 high risk patients (55 years of age or older), who had a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes plus at least one other cardiovascular risk factor and were not known to have low ejection fraction or heart failure, were randomized to either ramipril or placebo therapy. After 4.5 years, patients who received ramipril had a statistically significant 16% and 26% relative risk reduction in all cause-related mortality and cardiovascular-related mortality, respectively. There was also a 22% relative risk reduction in the combined endpoint of cardiovascular-related mortality, myocardial infarction or stroke in patients who received ramipril.²⁴ These results are similar to those observed in the present investigation although the magnitude of the effect

observed in the present investigation is considerably larger as compared to the HOPE study results.

Although not a clinical endpoint of the present investigation and contrary to other studies, ACE inhibitor therapy was not associated with a statistically significant reduction in total non-fatal cardiovascular-related hospitalizations, after adjusting for age, sex, CDS and drug therapies known to affect cardiovascular outcomes (531 and 194 non-fatal cardiovascular hospitalizations in the non ACE inhibitor and ACE inhibitor cohort, respectively ($p=0.531$)). The reason for this result is not known. It may be possible, however, that the use of ACE inhibitors for primary prevention in patients with diabetes does not affect the overall incidence of cardiovascular events experienced by patients. Instead, ACE inhibitors may influence the nature of those events. Patients receiving ACE inhibitors for primary prevention may experience a reduction in the proportion of cardiovascular events that are fatal events.

Results from the present investigation seem to support this. Despite ACE inhibitor therapy having a significant effect in reducing all cause-related mortality, fatal and non-fatal events combined, and cardiovascular-related mortality, the results on only non-fatal events are less favorable. Although non-fatal cardiovascular events were reduced in the ACE inhibitor cohort, this did not reach statistical significance. This suggests ACE inhibitors may influence the nature of the cardiovascular event experienced by the patient, but not the total number of cardiovascular events. It should be noted, however, that there were relatively fewer events for this outcome and thus there may have been insufficient statistical power to detect a difference.

Subgroup analysis of the MICRO-HOPE substudy also suggested that the benefits of ACE inhibitors may not be equally effective in reducing cardiovascular morbidity and mortality in all subsets of patients with diabetes. In particular, in a subgroup of patients with diabetes and at least one cardiovascular risk factor, but no established cardiovascular disease, no significant reduction in the risk for the combined endpoint of cardiovascular death, myocardial infarction or stroke was observed. This is despite a relatively large subgroup size ($n = 1,119$).²⁴ The results of the present investigation contradict those observed in the MICRO-HOPE subgroup analysis. In the present investigation, ACE inhibitor use was associated with a statistically significant reduction in the combined endpoint. The discrepancies between the two studies on other endpoints cannot be discussed, as they were not published in the MICRO-HOPE substudy.

Interestingly, other subgroups of patients in the MICRO-HOPE substudy also appeared to derive little benefit from therapy with ramipril. In particular, in patients receiving either insulin, either as monotherapy ($n = 1,852$) or in combination with oral hyperglycemics ($n = 180$), no significant risk reduction in the combined endpoint was observed although the numbers of patients in the combination group were relatively small.

The results of the present investigation appear to support these observations in the MICRO-HOPE substudy. In a subgroup of patients receiving insulin therapy ($n = 743$), representing 12% of the entire cohort, the adjusted HR (95% CI) for the combined endpoint after controlling for age, sex, chronic diseases score (CDS) and drug therapies known to affect cardiovascular outcomes, was 0.88 (0.47 – 1.67). Suggesting, that similar to the results observed in the MICRO-HOPE substudy, patients receiving insulin therapy

may not derive as great of benefit from ACE inhibitor therapy as compared to patients not receiving insulin therapy in relation to fatal and non-fatal events combined.

It is important to realize, however, that the subgroup analyses for insulin users were not primary or secondary endpoints in either the MICRO-HOPE study or in the present investigation. As well, the MICRO-HOPE subgroup analyses were conducted using data from a previous subanalysis of the larger HOPE study. In both studies, there were also a disproportionate number of subjects exposed and not exposed to the drugs in question. In the MICRO-HOPE subgroup analyses, only 9.9% and 19.3% of patients included were receiving placebo therapy in the no cardiovascular disease and insulin therapy subgroups, respectively. In the present investigation, only 21% of patients were receiving active therapy with ACE inhibitors in the insulin subanalysis. As a result, the validity of the observed effects in both the present investigation and in the MICRO-HOPE subgroup analyses may be questioned.

As indicated above, interpretation of the results observed in the present investigation with previously completed studies is difficult. The inclusion criteria between previous studies and the present investigation are significantly different. All of the above mentioned studies evaluate the use of ACE inhibitors for secondary prevention only. The present investigation was designed to evaluate the use of ACE inhibitors for primary prevention of cardiovascular morbidity and mortality. In the previously conducted studies, patients with existing cardiovascular disease have been included in the study. Although the HOPE study is often considered as a study on the use of ACE inhibitors for primary prevention, it can only be viewed as evidence for secondary prevention. Approximately 80% of individuals enrolled in the HOPE study had a history

of coronary heart disease, with a significant proportion having a history for myocardial infarction upon enrolment into the study. As a result, a fair comparison between ACE inhibitor therapies for primary prevention versus secondary prevention cannot be made.

Comparisons between the results seen in the present investigation and previous research are also difficult to complete due to the treatments under comparison. Most of the previous studies, with the exception of the GISSI-3, TRACE, and HOPE studies, have evaluated the benefits of ACE inhibitors in comparison to other active therapies. In the present investigation, ACE inhibitor therapy was not compared to any other active therapies. Differences observed between two active therapies are likely to be smaller than differences observed between an exposure to an active therapy versus placebo or no exposure. It has been suggested that the results observed between two active therapies may be 10% lower than those observed between active therapy and placebo or non exposure.²⁴ As a result, even though the results observed in the present investigation are somewhat higher than those observed in randomized controlled trials, this may be due in part to the therapies under comparison.

Of the studies that have evaluated the effects of ACE inhibitor therapy versus placebo, the HOPE study provides the best comparative trial for the results observed in the present investigation. In comparing the two study results, although both studies support the use of ACE inhibitors to reduce the risk of all cause-related mortality and cardiovascular related mortality, the magnitude of the observed effects are considerably larger in the present investigation. This may be due in part to several possible reasons. In the HOPE study, only approximately 40% of individuals included in the study had diabetes while in the present investigation all patients had diabetes. Patients with diabetes

may benefit more from the additional of ACE inhibitor therapy as compared to patients without diabetes. Results from the MICRO-HOPE substudy, which only included patients with diabetes, appears to support this. In the HOPE study, there was a 16%, 22%, and 26% relative risk reduction in all cause-related mortality, the combined endpoint (myocardial infarction, stroke or cardiovascular death), and cardiovascular related mortality, respectively. In the MICRO-HOPE substudy, however, in the 3,654 patients with diabetes, the use of ramipril was associated with a 24%, 25%, and 37% relative risk reduction in the same endpoints, respectively.

Other studies have also shown an increased benefit of ACE inhibitor therapy in patients with diabetes. For example, in the CAPPP study, analysis of all participants showed there was a non-statistically significant 5% increase and a statistically significant 23% and 7% relative risk reduction in the combined endpoint (fatal and non-fatal myocardial infarction, fatal and non-fatal stroke, and other cardiovascular-related deaths), cardiovascular-related mortality and all cause-related mortality, respectively, for captopril compared to conventional therapy. In the CAPPP subanalysis, which only included patients who had diabetes, the observed results were very different. In the 572 patients from the CAPPP participants who had diabetes, there was a statistically significant 41%, 52% and 46% relative risk reduction in the combined endpoint, cardiovascular-related mortality and all cause-related mortality, respectively, for captopril compared to conventional therapy.

The increased magnitude of the observed effects in the present investigation compared to the HOPE and MICRO-HOPE substudy may possibly be due to the inclusion criteria used in the studies. In the MICRO-HOPE substudy, patients in the

ramipril treated group had a mean duration of diabetes of 11.1 years prior to the initiation of ramipril therapy. In the present investigation, ACE inhibitor therapy was initiated, on average, within 2 years following the initiation of oral antidiabetic medication. Although it is unknown when the diagnosis of diabetes occurred in the present investigation, it was designed to observe the effects of ACE inhibitors in new users of oral antidiabetic agents; that is, patients with no previous exposure to oral antidiabetic medications and presumably with relatively new onset hyperglycemia. This possible discrepancy in duration of diabetes may influence the outcomes observed in the two studies.

Diabetes is known to be a chronic progressive disease. As a result, patients in the HOPE and MICRO-HOPE substudy presumably had more clinically advanced diabetes than individuals included in the present investigation.¹⁸³ As indicated previously, only 20% of individuals were free of cardiovascular disease at baseline in the HOPE study while all participants in the present investigation were relatively free of cardiovascular disease at baseline. The addition of ramipril therapy early in the progression of diabetes before cardiovascular disease has been established may have provided greater benefits for patients with diabetes.

5.2 Study Limitations

Since the present investigation was based on the administrative databases of Saskatchewan Health, there are several inherent limitations to both the internal validity and external validity of the results:

5.2.1 Internal Validity

5.2.1.1 Lack of Direct Clinical Information

Due to the nature of the Saskatchewan Health databases, there is limited direct clinical information regarding subject's baseline cardiovascular risk and modifiable cardiovascular risk factors (e.g., glycemic control, hypertension, lipids, smoking, body mass index (BMI), and exercise). Subjects in the ACE inhibitor cohort may have had a lower baseline risk for all cause-related mortality and non-fatal and fatal cardiovascular events. Since the analysis was based entirely on the administrative databases, we could not control directly for all of these factors.

Control for baseline cardiovascular risk was undertaken to a certain extent by excluding from the study cohorts all subjects who had a hospital separation for any cardiovascular disease in the 3 years prior to their oral antidiabetic index date. Subjects in the ACE inhibitor cohort were also excluded for a hospital separation for any cardiovascular disease occurring between their oral antidiabetic index date and their ACE inhibitor index date. Furthermore, both new and established ischemic heart disease and congestive heart failure was partially controlled for in our analysis. All subjects in the non ACE inhibitor cohort were excluded if a prescription claim for a product containing nitroglycerin or a loop diuretic occurred prior to their oral antidiabetic index date. Subjects in the ACE inhibitor cohort were also excluded if a prescription claim for these products occurred prior to their ACE inhibitor index date. As a result, presumably, subjects in the non ACE inhibitor cohort were relatively free of cardiovascular disease, including ischemic heart disease and congestive heart failure, for an average of 3 years prior to their oral antidiabetic index date. Subjects in the ACE inhibitor cohort were

relatively free of cardiovascular disease, including ischemic heart disease and congestive heart failure, for an average of 5 years prior to their ACE inhibitor index date.

In addition, both nitroglycerin and loop diuretics were included in the analysis to control for the presence of ischemic heart disease and congestive heart failure following the study index date and ACE inhibitor index date for subjects in both the control and ACE inhibitor cohort, respectively. Nitroglycerin and loop diuretics were used as markers for ischemic heart disease and congestive heart failure, respectively, as both have been shown to be strong indicators for the diagnosis of these diseases.^{172;174;175} As a result, we were able to partially control for both new and established cardiovascular disease in our analysis.

In the present investigation, significantly more subjects in the ACE inhibitor cohorts had prescription claims for both nitroglycerin and loop diuretics throughout the follow-up period. This would suggest that more subjects in the ACE inhibitor cohort had a clinical diagnosis of ischemic heart disease and congestive heart failure. Based on the hospitalization dataset, there is some evidence to support this. More subjects in the ACE inhibitor cohort had hospital separation histories for ischemic heart disease and congestive heart failure based on ICD-9 coding of the separations. A total of 3.3% and 4.7% of subjects in the control and ACE inhibitor cohorts, respectively, had hospital separations with an ICD-9 code for ischemic heart disease. There were also a total of 1.2% and 2.9% of subjects in the control and ACE inhibitor cohorts, respectively, which had hospital separations with an ICD-9 code for congestive heart failure. Even though ACE inhibitors improve survival in patients with established coronary heart disease and congestive heart failure, they are still associated with high mortality and morbidity. For

instance, after a clinical diagnosis of congestive heart failure, the median survival is 1.7 years in men and 3.2 years in women.¹⁸⁴ Congestive heart failure is also the leading cause of hospitalization in patients over the age of 65.¹⁸⁵

Since the hospital separation dataset indicates more individuals in the ACE inhibitor cohort had separations for both ischemic heart disease and congestive heart failure, as well as, more dispensations for nitroglycerin and loop diuretics, we would have expected subjects in the ACE inhibitor cohort to be at a somewhat higher risk compared to the non ACE inhibitor cohort. The risk to an individual with ischemic heart disease or congestive heart failure receiving ACE inhibitor therapy would be presumably higher compared to an individual without these diseases. We therefore would have expected an increase in mortality in the ACE inhibitor cohort if ACE inhibitors are ineffective for primary prevention, but, in fact, we observed the opposite.

It is also possible that the observed effects were due to other modifiable risk factors. First, the observed difference in outcomes may have been due to differential blood pressure control between the study groups. Results from the HOPE and MICRO-HOPE studies indicated that blood pressure was decreased slightly more in the subjects receiving ramipril compared to placebo therapy. The decrease in blood pressure, however, was very small and was deemed unlikely to account for the large reduction in clinical endpoints observed in the study.²⁴ In the present investigation, blood pressure values were not available. We did attempt to partially control for blood pressure by including common drug therapies used in the treatment of hypertension in the multivariate analysis. Based on the characteristics of the subjects analyzed in the present investigation, it is unlikely that differential blood pressure control is responsible for the

results observed. There were significantly more subjects in the ACE inhibitor cohort who had dispensations of medications used to treat hypertension such as beta-blockers, calcium channel blockers and diuretics.

Due to the lack of direct clinical information within the datasets, we do not know for what particular diagnosis or disease these agents were prescribed. Beta-blockers and calcium channel blockers can be used for many different indications and may not have been prescribed for hypertension. Diuretics (excluding loop diuretics), however, are almost exclusively prescribed for the treatment of hypertension. This potentially suggests that subjects in the ACE inhibitor cohort may have had a higher incidence of hypertension compared to the non ACE inhibitor cohort. If this were the case, we would have, again, expected an increased mortality in the ACE inhibitor cohort. It is possible, however, that the subjects in the ACE inhibitor cohort may have had a higher incidence of treated hypertension compared to the non ACE inhibitor cohort. As a result, subjects in the ACE inhibitor cohort may have had a greater chance of having their blood pressure controlled and therefore a decreased risk for mortality, rather than a higher incidence of hypertension and increased risk of mortality.

Second, the observed differences in outcomes may have been due to differences in body mass index (BMI) between the study groups. BMI is a strong risk factor for the development of cardiovascular disease, especially in patients with diabetes.¹¹² No specific variable was included in the analysis to control for the potential differential effects of BMI on cardiovascular outcomes. This is because no variables in an administrative dataset can be used as a reliable indicator for BMI, height or weight. Research has suggested, however, that in patients with type 2 diabetes, metformin may be more likely

to be prescribed in individuals who are obese due to better patient outcomes.^{74,75} In the present investigation, more subjects in the ACE inhibitor cohort had prescription claims for metformin compared to the non ACE inhibitor cohort. This suggests that there may have been a higher incidence of obesity within the ACE inhibitor cohort. If this were the case, we would have expected an increased mortality in the ACE inhibitor cohort.

Third, the observed differences in outcomes may have been due to differences in glycemic control. Several observational studies have suggested that poor glycemic control may be associated with the development of cardiovascular disease in individuals with diabetes.^{93,112,123-125} It is possible, patients in the non ACE inhibitor cohort had poorer glycemic control compared to those in the ACE inhibitor cohort. All subjects, however, were receiving oral antidiabetic therapy. During the period of time of this investigation (i.e., the 1990's), sulfonylureas and metformin were the main medications available for use in patients with diabetes. Alpha-glucosidase inhibitors were not available in Saskatchewan until the late 1990's and meglitinides and thiazolidinediones were not readily available until early in the 2000's. The majority of oral antidiabetic agents prescribed to patients with diabetes in Saskatchewan would have been for a sulfonylurea or metformin. Sulfonylureas and metformin are equipotent in terms of lowering blood glucose levels.⁷⁰ As a result, there is no reason to assume that glycemic control was poorer in the non ACE inhibitor cohort. Furthermore, there is currently little evidence to support that improvement in blood glucose levels leads to reductions in cardiovascular events or complications. There have been several randomized controlled trials assessing whether tight glycemic control improves macrovascular outcomes in patients with diabetes.^{39,42,59,127} To date, no study has shown that improvements in

glycemic control leads to improvement in macrovascular outcomes. It is therefore unlikely the results observed were a result of differences in glycolic control.

Although mentioned briefly in the preceding discussion, the observed differences between the two groups may have also been related to the presence of comorbidities. We have attempted to control for this by assessing the burden of concurrent comorbidities using a modified chronic disease score (CDS) and other drug therapies that may influence cardiovascular outcomes and including these as covariates in the multivariate analysis. It is acknowledged that not all comorbidities would be captured with the use of the CDS; however, a significant proportion of the major comorbidities that affect patient outcomes would have been captured. In addition, specific drug therapies such as cholesterol therapy and ASA therapy were also included in the analysis to control for any possible differences in comorbidities between study groups. Based on the CDS and medication prescription claims, it is unlikely differences in comorbidities were responsible for the observed effects. Subjects in the ACE inhibitor cohort had a significantly higher CDS score compared to those in the non ACE inhibitor cohort. As well, there were also significantly more subjects in the ACE inhibitor cohort who had prescription claims for medications known to affect cardiovascular outcomes. This would suggest that patients in the ACE inhibitor cohort would be at an increased risk of mortality compared to the non ACE inhibitor cohort. If this were the case, we would have expected an increased mortality in the ACE inhibitor cohort. The observed reduction in clinical events in the ACE inhibitor cohort would obviate these concerns.

5.2.1.2 Administrative Databases

Besides the lack of direct clinical information, there are also several limitations based solely on the administrative data collected. Although the SPDP provides comprehensive collection of drug dispensations including drug name, amount dispensed, dose, and dosage form, there is no method to ensure that the drugs were consumed by the subjects as prescribed. As a result, the drug dispensation data cannot ensure the level of drug exposure. Based on our inclusion criteria, however, all subjects in the ACE inhibitor cohort had to have received ACE inhibitors for a minimum of 1 year based on prescription refill records. Our analysis indicated that subjects received ACE inhibitors for an average of 3.6 years. We can therefore be reasonably confident that subjects had a sufficient exposure to ACE inhibitors throughout the follow-up period based on our ability to follow their prescription refills patterns.

Administrative databases are also limited by the potential for inconsistencies in the validity of the diagnoses based on hospital separation histories. The hospital separation system in Saskatchewan uses a 4-digit ICD-9 coding system to classify discharge diagnoses. Although three discharge diagnoses are included in the hospital services data, only the coding for the primary diagnoses was used in the present investigation. This diagnostic code may or may not have been the true reason for a subject's hospital admission. There is some evidence to suggest that hospital separation codes may not reliably capture the diagnosis of interest.

For example, in 1999, Liu *et al.* examined the validity of the diagnosis of stroke on hospital discharge records in Saskatchewan. They concluded that hospital separation files in Saskatchewan for the diagnosis of stroke should be used with caution. They found

that the use of a primary diagnosis with all stroke ICD-9 categories (430-438) only had a positive predictive value of 45% for occurrence of a definite acute stroke in tertiary-care hospitals.¹⁸⁶ These ICD-9 codes are also the categories used in the present study. As a result, the lack of a statistically significant effect in the endpoint of non-fatal myocardial infarction and non-fatal stroke may be due to inconsistencies in ICD-9 coding for stroke hospital admissions. It should be noted, however, that the Saskatchewan Health databases have been used in numerous epidemiological studies evaluating outcomes with drug use and are considered to be comprehensive and high quality data.^{168,187-189} The validity of ICD-9 coding will be a concern for the validity of the cardiovascular-specific outcomes. For this reason, we chose all cause-related mortality as the primary outcome; there can be very little debate for such an outcome. The consistency of results for cardiovascular-specific outcomes with all cause-related mortality increases our confidence in these outcomes.

5.2.2 External Validity

5.2.2.1 Exclusion of Sub-populations

Due to the nature of the Saskatchewan Health coverage, certain patient sub-populations were not included in the present investigation. Approximately 5% of individuals within the province of Saskatchewan are not included in the Health Insurance Registration File (HIRF). This group is mainly composed of individuals who receive federal health coverage, including members of the Royal Canadian Mounted Police (RCMP), Canadian Forces, and federal penitentiary inmates.

In the present investigation, data on prescription claims were used to select subjects for inclusion into the study, as well as, to identify individuals exposed to ACE inhibitor therapy. In Saskatchewan, approximately 9% of the population is ineligible for coverage under the Saskatchewan Prescription drug Plan (SPDP). This segment of the population is mainly represented by the registered Indians who have their prescription drug costs covered by a Federal government agency. Since it is not possible to ascertain the exposure status in this group of subjects and therefore assess the impact of ACE inhibitor therapy on cardiovascular outcomes, they have been excluded from the present investigation.

The generalizability of the results may also be restricted since the present investigation was based entirely on information obtained from individuals with diabetes residing in the province of Saskatchewan. As a result, extrapolation of the results to other individuals residing outside of Saskatchewan should be done with caution. It is unlikely, however, that the results obtained are unique to residents of Saskatchewan and beneficiaries of Saskatchewan Health.

One of the strengths of the present investigation, however, is the limited exclusion criteria used in the present investigation. Compared to other randomized controlled trials evaluating ACE inhibitor in patients with diabetes, the inclusion and exclusion criteria of the present investigation provided a more diverse and heterogeneous group of individuals with diabetes. Some measure of confidence can be assured that the results may be applicable to a larger population of individuals as compared to those obtained from previous randomized controlled trials.

5.3 Study Implications

5.3.1 Implications for Clinical Practice

The results of the present investigation provide some insight into the potential benefits of ACE inhibitors used for primary prevention in individuals with type 2 DM. Although causality cannot be inferred, due to the observational design, there appears to be a strong association between the use of ACE inhibitors for primary prevention and reduced mortality in patients with type 2 diabetes.

In today's era of evidence-based medicine, many clinicians prefer to wait for evidence of efficacy from randomized controlled trials (RCTs) before changing their clinical practice. Despite the importance of RCTs in clinical policy decisions, however, it has been estimated that less than 20% of clinical policies are actually based on evidence from such studies.³⁸

Further, there are many instances in today's clinical practice where RCTs cannot be completed. The questions being addressed in the present investigation fall into this category. Although a RCT would provide the best possible evidence for the efficacy of ACE inhibitors for primary prevention in patients with type 2 DM, it could not be conducted due to ethical reasons.

Results from the HOPE and MICRO-HOPE studies have shown that ACE inhibitors are efficacious in patients with diabetes and established cardiovascular disease. In order to evaluate the present results with a RCT, patients with diabetes and no established cardiovascular disease would be required to be randomized to therapy with an ACE inhibitor or placebo. Once the patient develops cardiovascular disease, however, it would be unethical to withhold ACE inhibitor therapy in patients who were randomized

to the placebo arm based on the results of the HOPE and MICRO-HOPE studies. As a result, this type of research question can only be studied through the use of observational data.

It may be desirable to have the results of the present investigation confirmed with other observational studies. Until this is completed, however, this observational data provides the most valid information available to base decisions regarding clinical policy and supports the use of ACE inhibitors for primary prevention of cardiovascular events in patients with type 2 DM.

Observational studies, such as the present investigation, also help to address issues related to real world practice settings. In most randomized controlled trials, highly trained medical specialists are generally responsible for the care of the patient during the trial period. For example, the HOPE study was largely conducted by physicians specializing in cardiology or related fields. As a result, the type of care received during the trial may not accurately reflect real world practice. This may potentially have a large impact on the generalizability of the results to a real world setting. In the present investigation, most prescribing would have been conducted by general practitioners and family physicians. As a result, more confidence may be gained in the fact that the results may represent what would be expected in a real world practice setting. Furthermore, the results of our study also strongly suggest that ACE inhibitors used for primary prevention are safe in a wide range of patients with type 2 diabetes.

5.3.2 Implications for Future Research

In order for decision makers to make more informed decisions regarding the use of ACE inhibitors for primary prevention in patients with type 2 DM, in the absence of RCT evidence, more observational studies in other populations of patients with type 2 DM will be required. In addition, the use of other epidemiological techniques to control for potential allocation bias and risk adjustments should be completed within the current dataset. In particular, the use of propensity scoring (i.e., corrected group prognosis method) may further address issues of allocation bias.

A propensity score represents the likelihood of receiving a particular therapy given the individuals baseline characteristics and thereby helps to better estimate the causal effects in large datasets.¹⁹⁰ The use of propensity scoring allows researchers the opportunity to adjust for potential allocation bias in observational studies where randomization is not possible.¹⁹¹ The use of propensity scoring in the current dataset would increase the confidence in the validity of the results by controlling for any allocation bias observed in the study.

5.4 Conclusion

Over the last decade, advancements into the treatment of type 2 DM have reduced many of the complications of the disease. Unfortunately, there has been little progress into the prevention and treatment of cardiovascular disease in patients with type 2 DM. Cardiovascular complications of the disease are still associated with significant morbidity and mortality in patients with diabetes. New treatment strategies are reducing the impact cardiovascular diseases are having on patients with type 2 DM. Most notably, there is

increasing evidence that ACE inhibitors are beneficial for secondary prevention in patients with type 2 DM. There is little evidence, however, to support the use of ACE inhibitors for primary prevention.

Studies such as the present investigation can help to provide the necessary evidence for the use of ACE inhibitors for primary prevention in patients with diabetes. Although randomized controlled trials can provide the strongest evidence for efficacy of new treatment strategies, they may not always be feasible. In cases such as this, observational studies are required to provide the best available evidence to help inform and direct clinical decisions.

In this observational study, ACE inhibitor use was associated with significant reductions in all cause-related mortality, cardiovascular-related mortality, and in the combined endpoint of fatal and non-fatal events in subjects with diabetes, despite obvious increased risk of these events in ACE inhibitor users. There was also a trend towards reduction in non-fatal myocardial infarction or non-fatal stroke in patients who used ACE inhibitors.

In the present investigation, subjects were relatively free of cardiovascular disease at baseline and were therefore at a considerably lower risk for major cardiovascular events compared to the participants from randomized controlled trials with established cardiovascular disease. Despite this, ACE inhibitor therapy was still associated with cardiovascular risk reduction in our study. This strongly suggests that all patients with type 2 diabetes may benefit from the addition of ACE inhibitor therapy irrespective of the patient's cardiovascular risk.

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Appendix A - Marketed Oral Antidiabetic Agents and Insulin Products in Canada

Oral Antidiabetic Agents

Sulfonylureas

Chorpropamide (Diabinese®)
Gliclazide (Diamicon®; Diamicon MR®)
Glyburide (Diabeta®)
Tolbutamide (Orinase®)

Biguanides

Metformin (Glucophage®)

Alpha-Glucosidase Inhibitors

Acarbose (Prandase®)

Thiazolidinediones

Rosiglitazone (Avanadia®)
Pioglitazone (Actos®)

Carbamoyl Benzoic Acid Derivatives

Repaglinide (Gluconorm®)
Nateglinide (Starlix®)

Insulin Products

Rapid Acting

Insulin lispro (Humalog®)
Insulin aspart (Novorapid®)

Short-acting or Regular Insulin

Humulin R®
Novolin ge Toronto®
Iletin II R®

Intermediate-acting or NPH Insulin

Humulin N®
Novolin ge NPH®
Iletin II NPH®

Premixed Insulin

Humulin 20/80; 30/70®
Novolin ge 10/90; 20/80; 30/70; 40/60;
50/50®
Humalog Mix25®

Intermediate-acting or Lente Insulin

Humulin L®
Novolin ge Lente®
Iletin II Lente®

Longer-acting or Ultra Lente Insulin

Humulin U®
Novolin ge Ultralente®
Iletin II Ultralente®
Insulin Glargin Lantus®

Appendix B - Major Clinical Trials Evaluating Angiotensin-Converting Enzyme Inhibitors on Cardiovascular Morbidity and Mortality with Diabetic Subanalyses

1. Acute Myocardial Infarction

Study Name	Comparison	Total Number of Diabetics Enrolled (% of Total Patients Enrolled)	Mean Follow-Up Duration	Results
GISSI-3 ²⁸	Lisinopril ± NTG vs placebo	2790 (15%)	6 weeks	<i>Primary endpoint</i> - SS reduction in all cause mortality (OR 0.68; 95% CI, 0.53 – 0.86; p<0.025); <i>Secondary endpoint</i> - NSS reduction in combined endpoint of mortality + development of CHF (OR 0.85; 95% CI, 0.71 – 1.01; p>0.05)
TRACE ²³	Trandolopril vs placebo	237 (14%)	26 months	<i>Primary endpoint</i> - SS reduction in all cause mortality (RR 0.64; 95% CI, 0.45 – 0.91; p<0.05); <i>Secondary endpoints</i> - SS reduction in cardiovascular death (RR 0.56; 95% CI, 0.37 – 0.85; p=0.01); - SS reduction in sudden death (RR 0.46; 95% CI, 0.25 – 0.85; p=0.01); - NSS reduction in reinfarction (RR 0.55; 95% CI, 0.29 – 1.07; p=0.08); - SS reduction in progression to CHF (RR 0.38; 95% CI, 0.21 – 0.67; p<0.001)

CI = confidence interval; OR = odds ratio; RR = relative risk; NTG = nitroglycerin; CHF = congestive heart failure;
 SS = statistically significant; NSS = not statistically significant

2. Hypertension

Study Name	Comparison	Total Number of Diabetics Enrolled (% of Total Patients Enrolled)	Mean Follow-Up Duration	Results
ABCD ²²	Nisoldipine vs Enalapril	470 (100%)	67 months	<i>Secondary endpoints</i> - SS increase in fatal or non-fatal MI for nisoldipine (RR 5.5; 95% CI, 2.1 – 14.6; p=0.001); - SS increase in non-fatal MI for nisoldipine (RR 4.8; 95% CI, 1.8 – 12.8; p=0.001); - NSS difference in cerebrovascular accident for nisoldipine (RR 1.6; 95% CI, 0.6 – 4.2; p>0.05); - NSS difference in development of CHF for nisoldipine (RR 1.2; 95% CI, 0.4 – 4.0; p>0.05); - NSS difference in CV mortality for nisoldipine (RR 2.0; 95% CI, 0.7 – 6.1; p>0.05); - NSS difference in all cause mortality for nisoldipine (RR 1.3; 95% CI, 0.6 – 2.8; p>0.05); <i>Primary endpoints</i> - SS reduction in combined endpoint of fatal and non-fatal MI, stroke, other CV mortality (RR 0.59; 95% CI, 0.38 – 0.91; p=0.018); - NSS difference in CV mortality (RR 0.48; 95% CI, 0.21 – 1.10; p>0.05); - NSS difference in fatal and non-fatal stroke (RR 1.02; 95% CI, 0.55 – 1.87; p=0>0.05); - SS reduction in fatal and non-fatal MI (RR 0.34; 95% CI, 0.17 – 0.67; p=0.002);
CAPPP ²⁵	Captopril vs Conventional Therapy (Diuretics and/or β - Blockers)	572 (5%)	6 years	

STOP-2 ⁹	Enalapril/Lisinopril vs Conventional Therapy (β -Blockers and/or Diuretics) or Felodipine/Isradipine	719 (10.9%)	60 months	<i>Secondary endpoints</i> - SS reduction in all cause mortality (RR 0.54; 95% CI, 0.31 – 0.95; $p=0.034$); - SS reduction in all CV events (RR 0.67; 95% CI, 0.46 – 0.96; $p=0.029$)
				<i>Primary endpoints- Verses Conventional Therapy</i> - NSS reduction in CV mortality (RR 0.91; 95% CI, 0.59 – 1.40; $p>0.05$);
				<i>Secondary endpoints - Verses Conventional Therapy</i> - NSS reduction in fatal or non-fatal MI (RR 0.68; 95% CI, 0.37 – 1.26; $p>0.05$); - NSS reduction in fatal and non-fatal stroke (RR 0.88; 95% CI, 0.56 – 1.40; $p>0.05$); - NSS reduction in all cause mortality (RR 0.88; 95% CI, 0.62 – 1.26; $p>0.05$); - NSS reduction in all CV events (RR 0.85; 95% CI, 0.62 – 1.18; $p>0.05$)
				<i>Primary endpoints- Verses Calcium Channel Blockers</i> - NSS difference in CV mortality (RR 1.19; 95% CI, 0.75 – 1.89; $p>0.05$);

FACET ²⁶	Fosinopril vs Amlodipine	380 (100%)	2.5-3.5	<i>Secondary endpoints - Verses Conventional Therapy</i> - SS reduction in fatal or non-fatal MI (RR 0.51; 95% CI, 0.28 - 0.92; p=0.025); - NSS difference in fatal and non-fatal stroke (RR 1.16; 95% CI, 0.71 - 1.91; p>0.05); - NSS difference in all cause mortality (RR 1.14; 95% CI, 0.78 - 1.67; p>0.05); - NSS difference in all CV events (RR 0.94; 95% CI, 0.67 - 1.32; p>0.05) <i>Secondary endpoints</i> - SS reduction in combined endpoint of stroke, MI, angina requiring hospitalization (HR = 0.49; 95% CI, 0.26 - 0.95; p = 0.03); - SS reduction in combined endpoint of non-fatal and fatal stroke or MI (HR = 0.58; 95% CI, 0.30 - 1.13.95; p = 0.03); - NSS difference in non-fatal or fatal stroke (HR = 0.39; 95% CI, 0.12 - 1.23; p > 0.05); - NSS difference in non-fatal or fatal MI (HR = 0.77; 95% CI, 0.34 - 1.75; p > 0.05); - SS reduction in any major vascular event or procedure (HR = 0.49; 95% CI, 0.26 - 0.95; p = 0.03); - SS reduction in any death or any vascular event or any procedure (HR = 0.56; 95% CI, 0.32 - 0.97; p = 0.036); <i>Primary endpoints</i> - NSS difference in any diabetes related endpoint (RR 1.10; 95% CI, 0.86 - 1.41; p>0.05); - NSS difference in mortality related to diabetes (RR 1.27; 95% CI, 0.82 - 1.97; p>0.05); - NSS difference all cause mortality (RR 1.14; 95% CI, 0.81 - 1.61; p>0.05);
UKPDS 39 ²⁷	Captopril vs Atenolol	758 (100%)	9 years	

ALLHAT ¹⁶⁷	Lisinopril vs Chlorthalidone	8740 (36%)	4.9 years	<i>Secondary endpoints</i>	
				- NSS difference in MI (RR 1.20; 95% CI, 0.82 – 1.76; $p > 0.05$);	
				- NSS difference in stroke (RR 1.12; 95% CI, 0.59 – 2.12; $p > 0.05$);	
				- NSS difference in peripheral vascular disease (RR 1.48; 95% CI, 0.35 – 6.19; $p > 0.05$);	
				- NSS difference in microvascular disease (RR 1.29; 95% CI, 0.80 – 2.10; $p > 0.05$)	
				<i>Primary endpoints</i>	
				- NSS difference in non-fatal MI plus fatal CHD (RR 1.00; 95% CI, 0.87 – 1.14; $p > 0.05$);	
				<i>Secondary endpoints</i>	
				- NSS difference in all cause mortality (RR 1.02; 95% CI, 0.91 – 1.13; $p > 0.05$);	
				- NSS difference in stroke (RR 1.07; 95% CI, 0.0.90 – 1.28; $p > 0.05$);	
				- NSS difference in combined CHD (RR 1.03; 95% CI, 0.93 – 1.14; $p > 0.05$);	
				- NSS difference in combined CV disease (RR 1.08; 95% CI, 1.00 – 1.17; $p > 0.05$)	
				- SS difference in CHF (RR 1.22; 95% CI, 1.05 – 1.42; $p < 0.05$)	

CI = confidence interval; RR = relative risk; HR = hazards ratio; CHD = coronary heart disease; CHF = congestive heart failure; CV = cardiovascular; MI = myocardial infarction; SS = statistically significant; NSS = not statistically significant

3. Miscellaneous

Study Name	Comparison	Total Number of Diabetics Enrolled (% of Total Patients Enrolled)	Mean Follow-Up Duration	Results
MICRO- HOPE ²⁴	Ramipril vs Placebo	3577 (38%)	4.5 years	<i>Primary endpoints</i> - SS reduction in combined endpoint of MI, stroke, CV mortality (RR 0.75; 95% CI, 0.64 – 0.88; $p=0.0004$); - SS reduction in MI (RR 0.78; 95% CI, 0.64 – 0.94; $p=0.01$); - SS reduction in stroke (RR 0.67; 95% CI, 0.5 – 0.90; $p=0.0074$); - SS reduction in CV mortality (RR 0.63; 95% CI, 0.49 – 0.79; $p=0.0001$) <i>Secondary endpoints</i> - SS reduction in all cause mortality (RR 0.76; 95% CI, 0.63 – 0.92; $p=0.004$); - NSS difference unstable angina requiring admission (RR 0.00; 95% CI, 0.83 – 1.21; $p>0.05$); - NSS difference in CHF requiring admission (RR 0.99; 95% CI, 0.72 – 1.34; $p>0.05$); - SS reduction in revascularization (RR 0.83; 95% CI, 0.70 – 0.98; $p<0.031$); - SS reduction in overt nephropathy (RR 0.76; 95% CI, 0.60 – 0.97; $p=0.027$)

CI = confidence interval; RR = relative risk; CHF = congestive heart failure; CV = cardiovascular; MI = myocardial infarction;
SS = statistically significant; NSS = not statistically significant

Appendix C - Marketed ACE Inhibitors in Canada in 1999

Single Entity Products

Benazepril (Lotensin[®])

Captopril (Capoten[®])

Cilazapril (Inhibace[®])

Enalapril (Vasotec[®])

Fosinopril (Monopril[®])

Lisinopril (Zestril[®], Prinivil[®])

Perindopril (Coversyl[®])

Quinapril (Accupril[®])

Trandolopril (Mavik[®])

Ramipril (Altace[®])

Combination Products

Enalapril/Hydrochlorothiazide (Vaseretic[®])

Lisinopril/Hydrochlorothiazide (Zestoretic[®],
Prinzide[®])

Quinapril/Hydrochlorothiazide (Accuretic[®])

Appendix D - ICD-9 Codes for Underlying Cardiovascular Cause of Death

Rheumatic Disease	390-398
Hypertension	401-404
Myocardial Infarction	410
Other Ischemic Diseases	411-414
Diseases of Pulmonary Circulation	415-417
Congestive Heart Failure	428
Other Forms of Heart Disease	420-427, 429
Hemorrhagic Stroke	430-432
Ischemic Stroke	433-434
TIA's	435
Other Forms of Stroke	436-438
Atherosclerosis	440
Other Diseases of Arteries, Arterioles and Capillaries	441-444, 446-448

Appendix E - Drug Markers for Established Cardiovascular Disease

Loop Diuretics

Furosemide (Lasix[®])

Bumetanide (Burinex[®])

Chlorthalidone (Apo-Chlorthalidone[®])

Ethacrynic Acid (Edecrin[®])

Tolazamide (Tolinase[®])

Nitroglycerin Products

Transdermal Therapeutic System (Minitran[®], Trinipatch[®], Nitro-Dur[®])

Sublingual Tablets (Nitrostat[®])

2% Ointment (Nitrol[®])

Metered Dose Lingual Spray (Nitrolingual Spray[®])

Appendix F - Marker Drugs Used in Calculation of Chronic Disease Score

anticoagulants
antiarrhythmics
nitrates
other vasodilating agents
ACE inhibitors
calcium channel blockers (typically not used to treat hypertension)
loop diuretics
lipid lowering agents
beta blockers
other diuretics
calcium channel blockers used to treat hypertension
other antihypertensives
isoproterenol
beta adrenergic agents
xanthine agents
bronchodilators & mucolytics
epinephrine
glucocorticoids
gold salts, DMARDs & other RA agents
Parkinson's agents
anticonvulsants
cromoglycate, nasal glucocorticoids & nasal ipratropium
tretinoin
topical macrolides
H2 antagonists, proton pump inhibitors & other ulcer agents
miotics & other glaucoma agents
uric acid agents
ergot derivatives & other migraine agents
hemostatics

Appendix G - Disease Specific Drug Therapies Known to Affect Cardiovascular Outcomes

Thiazide Diuretics

Loop Diuretics

Nitroglycerin and its derivatives

β -Blockers

Calcium Channel Blockers

Antiplatelet Therapy (Ticlopidine, Clopidogrel, Acetylsalicylic Acid)

Lipid Lowering Agents

Antiarrhythmic Agents

Metformin

Insulin

Appendix H - Variable Dictionary from Saskatchewan Health for Subject File

Variable	Description	Position	Length	Type
STUDYID	subject identification number	1	7	character
SEX	sex 1 = male 2 = female	8	1	character
AGEGRP	age group at index date 1 = 30 - 64 years 2 = 65 years or older	9	1	character
INDEX	index date Reported as a perpetual date.	10	5	numeric
ENTRY	entry date Reported as a perpetual date.	15	5	numeric
EXIT	exit date Reported as a perpetual date.	20	5	numeric
DETH_FLG	death flag D = deceased at exit blank = alive at exit	25	1	character
SCORE	chronic disease score	26	2	character
COD	underlying cause of death	28	4	character

Appendix I - Outpatient Prescription Drug Categories from Saskatchewan Health

Category	Description
1	metformin
2	acetoexamide
3	chlorpropamide
4	glyburide
5	tolbutamide
6	tolazamide
7	acarbose
8	insulin
9	ticlopidine
10	enteric coated ASA
11	clopidogrel
12	pentoxifylline
13	epoetin
14	anticoagulants
15	antiarrhythmics
16	nitrates
17	other vasodilating agents
18	ACE inhibitors
19	calcium channel blockers (typically not used to treat hypertension)
20	loop diuretics
21	lipid lowering agents - broken out into categories 43 through 55 - see below
22	beta blockers
23	other diuretics
24	calcium channel blockers used to treat hypertension
25	other antihypertensives
26	isoproterenol
27	beta adrenergic agents
28	xanthine agents
29	bronchodilators & mucolytics
30	epinephrine
31	glucocorticoids
32	gold salts, DMARDs & other RA agents
33	Parkinson's agents
34	anticonvulsants
35	cromoglycate, nasal glucocorticoids & nasal ipratropium
36	tretinoin
37	topical macrolides
38	H2 antagonists, proton pump inhibitors & other ulcer agents

39	miotics & other glaucoma agents
40	uric acid agents
41	ergot derivatives & other migraine agents
42	hemostatics
43	atorvastatin
44	bezafibrate
45	cerivastatin
46	cholestyramine
47	clofibrate
48	colestipol
49	fenofibrate
50	fluvastatin
51	gemfibrozil
52	lovastatin
53	pravastatin
54	probucol
55	simvastatin

**Appendix J - Variable Dictionary from Saskatchewan Health for Outpatient
Prescription Claims File**

Variable	Description	Position	Length	Type
STUDYID	subject identification number	1	7	character
DATE	dispensing date Reported as a perpetual date.	8	5	numeric
RX_CAT	drug category See Drug Categories & Grouped Drug Categories tables.	13	3	character
QUANTITY	quantity dispensed	16	5	numeric
STRENGTH	strength Reported as mg per tablet.	21	8.4 implicit 4- place decimal	numeric
FORM	dosage form TAB = tablet	29	3	character
SPECLTY	prescribing physician speciality 1 = general practitioner 2 = other specialist 3 = endocrinologist 4 = unknown	32	1	character

Appendix K - Variable Dictionary from Saskatchewan Health for Hospital File

Variable	Description	Position	Length	Type
STUDYID	subject identification number	1	7	character
ADMIT	admission date Reported as a perpetual date.	8	5	numeric
DISCHARG	discharge date Reported as a perpetual date.	13	5	numeric
DAYSSTAY	length of stay	18	4	numeric
DC_TYPE	discharge type 1 = medical discharge 2 = discharged without medical authorization 3 = death/autopsy performed 4 = death/no autopsy 5 = transferred to hospital 6 = transferred to a geriatric centre 7 = transferred to a nursing home 9 = other A = transferred to a designated level 4 bed B = transferred to a nondesignated level 4 bed C = transferred to a level 6 bed within the same hospital D = discharged or transferred from the facility alive S = sign out; patient left the facility against medical advice blank = death or stillbirth	22	1	character
PRIM_DX	primary diagnosis	23	5	character

SEC_DX	secondary diagnosis	28	5	character
OTH_DX	other diagnosis	33	5	character
PROC1	procedure code 1	38	4	character
PROC2	procedure code 2	42	4	character
PROC3	procedure code 3	46	4	character
CLAIMTYP	type of stay 1 = inpatient 2 = day surgery	50	1	character

Appendix L.1 Crude Odds Ratios for Covariates & All Cause-Related Mortality

Covariate		Subjects with Endpoint / Total Subjects (%)	Odds Ratio (95% CI)	p Value
Sex	Female	356 / 2693 (13.2)	1.36 (1.18-1.57)	<0.001
	Male	599 / 3483 (17.2)		
Age	30-64	239 / 3711 (6.4)	5.95 (5.08-6.96)	<0.001
	≥ 65 yr	716 / 2465 (29.0)		
Antiplatelet Therapy	No	803 / 5521 (14.5)	1.78 (1.46-2.16)	<0.001
	Yes	152 / 655 (23.2)		
Antiarrhythmic Therapy	No	820 / 5809 (14.1)	3.54 (2.83-4.43)	<0.001
	Yes	135 / 367 (36.8)		
Beta-Blocker Therapy	No	837 / 5306 (15.8)	0.84 (0.68-1.03)	0.094
	Yes	118 / 870 (13.6)		
Calcium Channel Blocker Therapy	No	816 / 5256 (15.5)	0.97 (0.80-1.18)	0.747
	Yes	139 / 920 (15.1)		
Diuretic Therapy (Except Loop Diuretics)	No	841 / 5476 (15.4)	1.07 (0.87-1.33)	0.523
	Yes	114 / 700 (16.3)		
Loop Diuretic Therapy	No	689 / 5408 (12.7)	3.63 (3.07-4.30)	<0.001
	Yes	266 / 768 (34.6)		
Lipid Lowering Therapy	No	898 / 5292 (17.0)	0.34 (0.26-0.45)	<0.001
	Yes	57 / 844 (6.4)		
Nitroglycerin Therapy	No	862 / 5606 (15.4)	1.07 (0.85-1.36)	0.555
	Yes	93 / 570 (16.3)		
Metformin Therapy	No	553 / 2593 (21.3)	0.47 (0.41-0.54)	<0.001
	Yes	402 / 3583 (11.2)		
Insulin Therapy	No	830 / 5433 (15.3)	1.12 (0.91-1.38)	0.274
	Yes	125 / 743 (16.8)		

Appendix L.2 Crude Odds Ratios for Covariates & Combined Endpoint

Covariate		Subjects with Endpoint / Total Subjects (%)	Odds Ratio (95% CI)	p Value
Sex	Female	224 / 2693 (8.3)	1.34 (1.13-1.60)	0.001
	Male	379 / 3483 (10.9)		
Age	30-64	170 / 3711 (4.6)	4.44 (3.69-5.34)	<0.001
	≥ 65 yr	433 / 2465 (17.6)		
Antiplatelet Therapy	No	384 / 5521 (7.0)	6.72 (5.54-8.15)	<0.001
	Yes	219 / 655 (33.4)		
Antiarrhythmic Therapy	No	510 / 5809 (8.8)	3.52 (2.74-4.54)	<0.001
	Yes	93 / 367 (25.3)		
Beta-Blocker Therapy	No	434 / 5306 (8.2)	2.71 (2.23-3.29)	<0.001
	Yes	169 / 870 (19.4)		
Calcium Channel Blocker Therapy	No	436 / 5256 (8.3)	2.45 (2.02-2.98)	<0.001
	Yes	167 / 920 (18.2)		
Diuretic Therapy (Except Loop Diuretics)	No	500 / 5476 (9.1)	1.72 (1.37-2.16)	<0.001
	Yes	103 / 700 (14.7)		
Loop Diuretic Therapy	No	450 / 5408 (8.3)	2.74 (2.24-3.35)	<0.001
	Yes	153 / 768 (19.9)		
Lipid Lowering Therapy	No	514 / 5292 (9.7)	1.04 (0.82-1.32)	0.742
	Yes	89 / 884 (10.1)		
Nitroglycerin Therapy	No	436 / 5606 (7.8)	4.91 (4.00-6.03)	<0.001
	Yes	167 / 570 (29.3)		
Metformin Therapy	No	306 / 2593 (11.8)	0.68 (0.57-0.80)	<0.001
	Yes	297 / 3583 (8.3)		
Insulin Therapy	No	533 / 5433 (9.8)	0.96 (0.74-1.24)	0.736
	Yes	70 / 743 (9.4)		

Appendix L.3 Crude Odds Ratios for Covariates & Cardiovascular-Related Mortality

Covariate		Subjects with Endpoint / Total Subjects (%)	Odds Ratio (95% CI)	p Value
Sex	Female	111 / 2693 (4.1)	1.34 (1.06-1.71)	0.016
	Male	190 / 3483 (5.5)		
Age	30-64	65 / 3711 (1.8)	5.94 (4.49-7.85)	<0.001
	≥ 65 yr	236 / 2465 (9.6)		
Antiplatelet Therapy	No	244 / 5521 (4.4)	2.06 (1.53-2.78)	<0.001
	Yes	57 / 655 (8.7)		
Antiarrhythmic Therapy	No	250 / 5809 (4.3)	3.59 (2.60-4.95)	<0.001
	Yes	51 / 367 (13.9)		
Beta-Blocker Therapy	No	256 / 5306 (4.8)	1.08 (0.78-1.49)	0.659
	Yes	45 / 870 (5.2)		
Calcium Channel Blocker Therapy	No	246 / 5256 (4.7)	1.30 (0.96-1.75)	0.092
	Yes	55 / 920 (6.0)		
Diuretic Therapy (Except Loop Diuretics)	No	264 / 5476 (4.8)	1.10 (0.77-1.57)	0.591
	Yes	37 / 700 (5.3)		
Loop Diuretic Therapy	No	220 / 5408 (4.1)	2.78 (2.13-3.63)	<0.001
	Yes	81 / 768 (10.5)		
Lipid Lowering Therapy	No	282 / 5292 (5.3)	0.39 (0.24-0.62)	<0.001
	Yes	19 / 884 (2.1)		
Nitroglycerin Therapy	No	266 / 5606 (4.7)	1.31 (0.91-1.89)	0.14
	Yes	35 / 570 (6.1)		
Metformin Therapy	No	173 / 2593 (6.7)	0.52 (0.41-0.66)	<0.001
	Yes	128 / 3583 (3.6)		
Insulin Therapy	No	276 / 5433 (5.1)	0.65 (0.43-0.99)	0.042
	Yes	25 / 743 (3.4)		

Appendix L.4 Crude Odds Ratios for Covariates & Non-Fatal Myocardial Infarction and Non-Fatal Stroke

Covariate		Subjects with Endpoint / Total Subjects (%)	Odds Ratio (95% CI)	p Value
Sex	Female	134 / 2693 (5.0)	1.32 (1.06-1.64)	0.013
	Male	225 / 3483 (6.5)		
Age	30-64	117 / 3711 (3.2)	3.34 (2.67-4.20)	<0.001
	≥ 65 yr	242 / 2465 (9.8)		
Antiplatelet Therapy	No	178 / 5521 (3.2)	11.46 (9.13-14.39)	<0.001
	Yes	181 / 655 (27.6)		
Antiarrhythmic Therapy	No	297 / 5809 (5.1)	3.77 (2.80-5.08)	<0.001
	Yes	62 / 367 (16.9)		
Beta-Blocker Therapy	No	219 / 5306 (4.1)	4.46 (3.55-5.58)	<0.001
	Yes	140 / 870 (16.1)		
Calcium Channel Blocker Therapy	No	232 / 5256 (4.4)	3.47 (2.76-4.36)	<0.001
	Yes	127 / 920 (13.8)		
Diuretic therapy (Except Loop Diuretics)	No	283 / 5476 (5.2)	2.24 (1.71-2.92)	<0.001
	Yes	76 / 700 (10.9)		
Loop Diuretic Therapy	No	267 / 5408 (4.9)	2.62 (2.04-3.37)	<0.001
	Yes	92 / 768 (12.0)		
Lipid Lowering Therapy	No	283 / 5292 (5.3)	1.67 (1.28-2.17)	<0.001
	Yes	76 / 884 (8.6)		
Nitroglycerin Therapy	No	210 / 5606 (3.7)	9.09 (7.2-11.47)	<0.001
	Yes	149 / 570 (26.1)		
Metformin Therapy	No	160 / 2593 (6.2)	0.89 (0.72-1.11)	0.307
	Yes	199 / 2583 (5.6)		
Insulin Therapy	No	309 / 5433 (5.7)	1.20 (0.88-1.63)	0.255
	Yes	50 / 743 (6.7)		